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=> s immune tolerance
L1 33218 IMMUNE TOLERANCE

=> s l1 and infertility treatment
L2 1 L1 AND INFERTILITY TREATMENT

=> d l2 cbib abs

L2 ANSWER 1 OF 1 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2000016006 EMBASE Immunologic tests and treatments in patients with unexplained infertility, IVF-ET, and recurrent pregnancy loss. Stovall D.W.; Van Voorhis B.J.. Dr. D.W. Stovall, Department of Obstetrics/Gynecology, Div. of Reproductive Endocrinology, Virginia Commonwealth University, 1101 East Marshall Street, Richmond, VA 23298, United States. Clinical Obstetrics and Gynecology 42/4 (979-1000) 1999. Refs: 99.
ISSN: 0009-9201. CODEN: COGYAK. Pub. Country: United States. Language: English. Summary Language: English.

AB The role that autoantibodies play in infertility remains uncertain. There are conflicting data about the prevalence of autoantibodies in women with endometriosis. Certainly no one has demonstrated an association between the presence of antibodies in women with endometriosis and infertility. Despite intensive study, there is also no consensus on a role of autoantibodies to the zona pellucida as a cause of infertility. Recently, much attention has been focused on autoantibodies and infertility, particularly on phospholipid antibodies and their effect on IVF success rates. The published studies suggest that women with infertility have an increased prevalence of phospholipid antibodies compared with fertile women. The presence of these antibodies, however, has not been associated with a worsened prognosis for IVF cycles. Many questions remain to be answered. What is the cause of this apparently increased prevalence of autoantibodies in infertile women? Do these autoantibodies cause infertility, or are they merely associated with some other condition that is actually causative? Finally, can treatment of autoantibodies improve pregnancy rates in infertile couples after IVF or other

infertility treatments? One key factor in immune-directed therapy may be the gestational age at which one starts treatment. It may be that if one waits until after cardiac activity is established before therapy is initiated, this may select a group of patients who have a high probability of having a live birth. Therefore, when designing randomized trials, it may be important to begin therapy as soon as a pregnancy test is positive or at least by 5 weeks' gestation. Immunologic therapy has been directed at both autoimmune and suspected alloimmune-associated pregnancy wastage. Because the maternal-fetal **immune tolerance** that allows for maternal acceptance of embryonic implantation and growth is poorly understood, it also has been difficult to identify tests that can differentiate between alloimmune and nonimmune-associated pregnancy failure. The answers to these questions should be sought by carefully conducted trials with appropriate control groups. Subjecting patients to expensive testing and 'treatments' before these answers are known is not consistent with good scientific or medical practice.

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=> s l1 and intertility
L3            0 L1 AND INTERTILITY

=> s l1 and infertility
L4           69 L1 AND INFERTILITY

=> s l4 and TGF beta
L5            3 L4 AND TGF BETA

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L6            1 DUP REMOVE L5 (2 DUPLICATES REMOVED)

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L6   ANSWER 1 OF 1  EMBASE  COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
     on STN                                                DUPLICATE 1
2002388217  EMBASE  Transforming growth factor β - A mediator of immune
     deviation in seminal plasma. Robertson S.A.; Ingman W.V.; O'Leary S.;
     Sharkey D.J.; Tremellen K.P.. S.A. Robertson, Reproductive Medicine Unit,
     Department of Obstetrics, Adelaide University, Adelaide, SA 5005,
     Australia. sarah.robertson@adelaide.edu.au. Journal of Reproductive
     Immunology  57/1-2 (109-128)  31 Oct 2002.
     Refs: 57.
     ISSN: 0165-0378. CODEN: JRIMDR.
     Publisher Ident.: S 0165-0378(02)00015-3. Pub. Country: Ireland. Language:
     English. Summary Language: English.
AB   TGF.beta. is a potent immune deviating agent, driving
     active forms of immune tolerance in peripheral tissues
     through effects on the induction and resolution of inflammatory responses
     and phenotype skewing in antigen-presenting cells and lymphocytes. The
     TGF.beta. content of seminal plasma from human, rodent
     and livestock species is amongst the highest measured in biological
     fluids. The seminal vesicle gland is the principal source of TGF
     .beta. in the semen of mice, where its synthesis is regulated by
     testosterone. At insemination, seminal TGF.beta. is
     deposited in the female tract and is activated by acidic vaginal pH,
     enzymes of male or female tract origin, or through cleavage-independent
     processes involving conformational change after interaction with
     epithelial cell docking proteins. Seminal TGF.beta.
     has been shown to be a principal stimulating agent in the post-coital
     inflammatory response, and is likely to be essential for induction of
     immune tolerance to seminal antigens. As well as
     preventing aberrant immunity to spermatozoa, these events are implicated
     in priming an appropriate female immune response to embryo implantation,
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since many seminal antigens are shared by the conceptus. The cascade of immunological events elicited by seminal **TGF.beta.** may therefore explain epidemiological observations linking acute and cumulative exposure to semen with successful placental development and pregnancy outcome. Depending on whether the female tract has evolved mechanisms to discriminate seminal antigens from opportunistic pathogens, there may be a detrimental cost of seminal **TGF.beta.** in inhibiting protective immunity to agents of sexually transmitted disease including HIV. A better understanding of the significance and role of **TGF.beta.** in semen will facilitate development of novel therapies for immune-based **infertility** disorders. .COPYRGT. 2002 Published by Elsevier Science Ireland Ltd.

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L7 57 DUP REMOVE L4 (12 DUPLICATES REMOVED)

=> d l7 1-57 cbib abs

L7 ANSWER 1 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN
2004:215565 Method for reinstalling control system for antigenic homeostasis of mammalian organisms (effect of kukharchuk-radchenko-sirman). Kukharchuk, Oleksandr Leonidovich; Radchenko, Viktor Volodimirovich; Sirman, Viktor Mirchovich (Ukraine). PCT Int. Appl. WO 2004022079 A1 20040318 DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (Russian). CODEN: PIXXD2. APPLICATION: WO 2003-UA30 20030901. PRIORITY: UA 2002-97178 20020903.
AB The invention relates to medicine and biology and can be used for allotransplantation and xenotransplantation of organs and tissues for curing autoimmune diseases (glomerulonephritis, rheumatic arthritis, chronic active hepatitis), degenerative neuropathies when an autoimmune process is exhibited in the form of a main pathogenic component (Alzheimer disease, disseminated sclerosis, amyotropic lateral sclerosis etc.), immunological **infertility**, myocardial infarction, cerebral stroke, Parkinson disease, hypoplastic and aplastic anaemia, immune noncarrying of pregnancy, endocrine diseases associated with hypofunction of blood glands including diabetes, various forms of osteoporosis, virile and female climacteric, radiation sickness and other diseases of different aetiology. In order to induce **immune tolerance** to the alloantigens of a donor with the aid of embryonal pluripotent progenitor cells, the reinstallation of a control system for antigenic homeostasis of a recipient organism is carried out by intravenous injection of megadoses of embryonal pluripotent progenitor cells which produce a new basis for immunocompetent cells controlling the antigenic homeostasis of an organism.

L7 ANSWER 2 OF 57 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2004066172 EMBASE Central and peripheral autoantigen presentation in **immune tolerance**. Pugliese A.. Dr. A. Pugliese, Diabetes Research Institute, Univ. of Miami School of Medicine, 1450 NW 10th Avenue, Miami, FL 33136, United States. apuglies@med.miami.edu. Immunology 111/2 (138-146) 2004.
Refs: 86.
ISSN: 0019-2805. CODEN: IMMUAM. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Recent studies in both humans and experimental rodent models provide new insight into key mechanisms regulating tolerance to self-molecules. These recent advances are bringing about a paradigm shift in our views about tolerance to self-molecules with tissue-restricted expression. There is, indeed, mounting evidence that selected antigen-presenting cells (APCs) have the ability to synthesize and express self-molecules, and that such expression is critical for self-tolerance. Insulin is a key hormone produced exclusively by pancreatic β-cells and a critical autoantigen in type 1 diabetes. It provides an excellent example of a molecule with tissue-restricted expression that is expressed ectopically by APCs. The fact that APCs expressing insulin have been demonstrated in both thymus and peripheral lymphoid tissues suggests that they may play a role in insulin presentation in both the central and peripheral immune system. Experimental mice, in which insulin expression was altered, provide functional data that help to dissect the role of insulin presentation by APCs of the immune system. This review addresses recent literature and emerging concepts about the expression of self-molecules in the thymus and peripheral lymphoid tissues and its relation to self-tolerance.

L7 ANSWER 3 OF 57 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2003:351144 Document No.: PREV200300351144. ASRI at Yale - 23rd Annual Meeting, New Haven, CT, USA, June 18-22, 2003. Anonymous. American Journal of Reproductive Immunology, (June 2003) Vol. 49, No. 6, pp. 319-381. print.
Meeting Info.: ASRI at Yale - 23rd Annual Meeting. New Haven, CT, USA. June 18-22, 2003. American Society of Reproductive Immunology.
ISSN: 1046-7408 (ISSN print). Language: English.

AB This meeting on reproductive immunology consists of abstracts and papers written in English for 48 presentations and 47 posters. Session themes include maternal-fetal interface, genital tract, high-risk pregnancies, biotechnology, gynecologic oncology, and ovarian immunology. Selected topics include interleukin-10, chlamydial infections, trophoblast invasion, cytokine production by uterine cells, and phenoxodiol.

L7 ANSWER 4 OF 57 MEDLINE on STN

2002688951. PubMed ID: 12447413. Reproductive immunology: Immunity's pregnant pause. Pearson Helen. Nature, (2002 Nov 21) 420 (6913) 265-6. Journal code: 0410462. ISSN: 0028-0836. Pub. country: England: United Kingdom. Language: English.

L7 ANSWER 5 OF 57 MEDLINE on STN

2002080666. PubMed ID: 11807769. HLA-G expression in early embryos is a fundamental prerequisite for the obtainment of pregnancy. Fuzzi Beatrice; Rizzo Roberta; Criscuoli Luciana; Noci Ivo; Melchiorri Loredana; Scarselli Benedetta; Bencini Erica; Menicucci Adriana; Baricordi Olavio R. (Department of Gynecology, Perinatal Medicine and Human Reproduction, University of Florence, Florence, Italy.) European journal of immunology, (2002 Feb) 32 (2) 311-5. Journal code: 1273201. ISSN: 0014-2980. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB Different mechanisms mediated by the expression of the HLA-class Ib HLA-G products are suggested to account for the induction of **immune tolerance** against the paternal antigens of the fetus during pregnancy. Soluble HLA-G antigens, mainly produced by cytotrophoblast cells at the materno-fetal interface and circulating in the body fluids, show a capacity analogous to that of membrane-boundstructures to inhibit NK cells. In the present report we have investigated, using specific ELISA, the presence of sHLA-G molecules in culture supernatants of early embryos obtained by in vitro fertilization (IVF) before transfer. The data obtained from the analysis of 285 supernatants corresponding to 101 IVF procedures (43 IVF, 58 intracytoplasmic sperm injection) identify two groups of patients on the basis of sHLA-G antigen presence. No differences in clinical parameters were observed between the groups, but positive embryo implantations occurred only in women showing sHLA-G

molecules in culture supernatants (Fisher's exact p value 2.56 x 10(-3)). The results obtained indicate that expression of HLA-G products in embryo cells is a mandatory, but not sufficient, prerequisite for the development of pregnancy.

L7 ANSWER 6 OF 57 MEDLINE on STN DUPLICATE 1
2002628758. PubMed ID: 12385837. Transforming growth factor beta--a mediator of immune deviation in seminal plasma. Robertson Sarah A; Ingman Wendy V; O'Leary Sean; Sharkey David J; Tremellen Kelton P. (Reproductive Medicine Unit, Department of Obstetrics and Gynaecology, Adelaide University, South Australia, Australia.. sarah.robertson@adelaide.edu.au) . Journal of reproductive immunology, (2002 Oct-Nov) 57 (1-2) 109-28. Ref: 57. Journal code: 8001906. ISSN: 0165-0378. Pub. country: Ireland. Language: English.

AB TGFbeta is a potent immune deviating agent, driving active forms of **immune tolerance** in peripheral tissues through effects on the induction and resolution of inflammatory responses and phenotype skewing in antigen-presenting cells and lymphocytes. The TGFbeta content of seminal plasma from human, rodent and livestock species is amongst the highest measured in biological fluids. The seminal vesicle gland is the principal source of TGFbeta in the semen of mice, where its synthesis is regulated by testosterone. At insemination, seminal TGFbeta is deposited in the female tract and is activated by acidic vaginal pH, enzymes of male or female tract origin, or through cleavage-independent processes involving conformational change after interaction with epithelial cell docking proteins. Seminal TGFbeta has been shown to be a principal stimulating agent in the post-coital inflammatory response, and is likely to be essential for induction of **immune tolerance** to seminal antigens. As well as preventing aberrant immunity to spermatozoa, these events are implicated in priming an appropriate female immune response to embryo implantation, since many seminal antigens are shared by the conceptus. The cascade of immunological events elicited by seminal TGFbeta may therefore explain epidemiological observations linking acute and cumulative exposure to semen with successful placental development and pregnancy outcome. Depending on whether the female tract has evolved mechanisms to discriminate seminal antigens from opportunistic pathogens, there may be a detrimental cost of seminal TGFbeta in inhibiting protective immunity to agents of sexually transmitted disease including HIV. A better understanding of the significance and role of TGFbeta in semen will facilitate development of novel therapies for immune-based **infertility** disorders.

L7 ANSWER 7 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN
2001:776884 Document No. 136:307953 Control and impairment of immune privilege in the testis and in semen. Filippini, Antonio; Riccioli, Anna; Padula, Fabrizio; Lauretti, Paola; D'Alessio, Alessio; De Cesaris, Paola; Gandini, Loredana; Lenzi, Andrea; Ziparo, Elio (Departments of Histology and Medical Embryology, University of Rome "La Sapienza", Rome, 00161, Italy). Human Reproduction Update, 7(5), 444-449 (English) 2001. CODEN: HRUPF8. ISSN: 1355-4786. Publisher: Oxford University Press.

AB A review. It has long been known that the testis is an immunol. privileged site in the body, and that human seminal plasma possesses a generalized immunosuppressive activity. Multiple factors participate in the establishment of immunotolerance in the testis: the blood-tubular barrier; the local production of immunosuppressive mols. by Sertoli cells; and the Fas system as regulator of immunol. homeostasis in both physiol. and pathol. conditions. Cytokine-induced up-regulation of Fas as well as of integrin ligands, which are known to be specific binding mols. for lymphocytes on the Sertoli cell surface, indicates that the "nursing" cells of seminiferous epithelium might be important in the impairment of immune privilege, causing autoimmune orchitis. In addition, the soluble form of Fas-ligand protein present in the seminal plasma of infertile patients might suggest a role for this immunomodulatory protein in male

infertility. Finally, an understanding of the mechanisms underlying immune privilege in the testis and in semen might help to clarify how cells expressing "non-self" antigens (such as male gametes) can escape the immune system in both the male and female genital tracts.

L7 ANSWER 8 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN
2002:685299 Document No. 137:383428 Etiopathogenesis and diagnostics of antisperm antibody-mediated **infertility**. Chelmonska-Soyta, Anna (Pracownia Immunol. Rozrodu, Katedra Prewencji i Immunol. Weter., Wydz. Med. Weter., Akad. Rolnicza, Wroclaw, 50-375, Pol.). Diagnostyka Laboratoryjna, 37(3), 325-338 (Polish) 2001. CODEN: DLJNAQ. ISSN: 0867-4043. Publisher: Polskie Towarzystwo Diagnostyki Laboratoryjnej.
AB A review. The problem of immunol. **infertility** has been investigated for a long time. It was confirmed that antisperm antibodies impair the sperms function and reduce fertility. However, a lot of topics concerning the tolerance of sperm-specific antigens in men and women, the risk factors associated with sperm antigens recognition, antisperm antibody diagnosis and the evaluation of the results of the diagnostic tests remain unclear. Here, the author discusses the current literature on the etiol., pathogenesis, and particularly diagnosis and diagnostic indications in this immunol. mediated **infertility**.

L7 ANSWER 9 OF 57 MEDLINE on STN DUPLICATE 2
2001560280. PubMed ID: 11607848. Immunological tolerance of the human fetus. Gaunt G; Ramin K. (Rochester Methodist Hospital, Mayo Clinic, Rochester, Minnesota 55905, USA.) American journal of perinatology, (2001 Sep) 18 (6) 299-312. Ref: 101. Journal code: 8405212. ISSN: 0735-1631. Pub. country: United States. Language: English.
AB Why is the fetus not rejected as foreign tissue? The maternal and fetal immune systems temporarily coexist; both are precisely tuned to detect and reject foreign invasion and yet somehow achieve a symbiotic relationship. This mutual state of tolerance is obviously critical for carrying pregnancy to full term. Two active arms of the immune system maintain protection of the host: the first of these involves a humoral immune system in which foreign tissue invokes an antibody response by recognition of antigenic surfaces by the B-cell, the second arm involves cell-mediated immunity in which T-cells and natural killer (NK) cells seek out and destroy foreign tissue. Several mechanisms are thought to invoke the **immune tolerance** of the fetus. These include: absence of major histocompatibility complex (MHC)-I antigens, presence of unique human lymphocyte antigen (HLA) surface molecules, nonspecific reduction of systemic immunoreactivity, possible role of blocking antibody, expressions of complement regulatory proteins, and factors of locally reduced immunoreactivity. Ultimately, developing regimens to control these elements in the clinical setting may help us overcome preterm labor, **infertility**, and preeclampsia. Available evidence regarding **immune tolerance** of the human fetus, integrated into a workable model, and focused at an overview level are systematically reviewed in this article.

L7 ANSWER 10 OF 57 MEDLINE on STN
2000452963. PubMed ID: 11006166. Control of the immunological environment of the uterus. Robertson S A. (Department of Obstetrics and Gynaecology and The Reproductive Medicine Unit, University of Adelaide, Adelaide SA 5005, Australia.) Reviews of reproduction, (2000 Sep) 5 (3) 164-74. Ref: 93. Journal code: 9602351. ISSN: 1359-6004. Pub. country: ENGLAND: United Kingdom. Language: English.
AB The uterine immune axis holds the key to solving major problems in female reproductive health, including **infertility**, many pathologies of pregnancy, and sexually transmitted disease. The molecular determinants of tolerance and immunity in the reproductive tract are now being identified, and the governing principles are similar to those in other mucosal tissues. Cytokines are implicated as pivotal regulators at important 'decision-making' points in each phase of the induction and

elicitation of a response. Indeed, the flexibility to deal appropriately with antigens as disparate as infectious micro-organisms, spermatozoa and the conceptus is likely to be attributable to the sophistication of the cytokine network in driving immune deviation. A better understanding of the factors controlling the development of immune activity in the uterus, particularly the significance of the inductive cytokine environment in determining the destiny of T-lymphocyte responses, will assist the rational design of new therapeutic strategies to treat immune-based reproductive disorders.

L7 ANSWER 11 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN

1999:566216 Document No. 131:183879 HLA linked pre-eclampsia and miscarriage susceptibility gene. O'Brien, Margaret; Bermingham, John; Quane, Kathleen A.; Jenkins, David M.; McCarthy, Tommie V. (National University of Ireland, Ire.). PCT Int. Appl. WO 9943851 A1 19990902, 79 pp. DESIGNATED STATES: W: AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-IE12 19990225. PRIORITY: IE 1998-134 19980225; IE 1998-668 19980812.

AB The invention relates to the identification of a susceptibility gene for pre-eclampsia and eclampsia and provides methods and diagnostic kits for diagnosing susceptibility to normal pregnancy, pre-eclampsia, eclampsia, intrauterine growth retardation, miscarriage, or miscarriage-related **infertility**. The invention is based on analyzing HLA-G or HLA-G linked nucleic acid, or HLA-G protein or HLA-G mRNA or cells or mols. whose concentration changes as a result of HLA-G action. PCR primers are provided for diagnostic detection of polymorphisms at codon-93 and a insertion/deletion in exon 8 of the HLA-G gene. The invention also provides pharmaceutical compns. for and methods of treatment of the above conditions.

L7 ANSWER 12 OF 57 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2000016006 EMBASE Immunologic tests and treatments in patients with unexplained **infertility**, IVF-ET, and recurrent pregnancy loss. Stovall D.W.; Van Voorhis B.J.. Dr. D.W. Stovall, Department of Obstetrics/Gynecology, Div. of Reproductive Endocrinology, Virginia Commonwealth University, 1101 East Marshall Street, Richmond, VA 23298, United States. Clinical Obstetrics and Gynecology 42/4 (979-1000) 1999. Refs: 99.
ISSN: 0009-9201. CODEN: COGYAK. Pub. Country: United States. Language: English. Summary Language: English.

AB The role that autoantibodies play in **infertility** remains uncertain. There are conflicting data about the prevalence of autoantibodies in women with endometriosis. Certainly no one has demonstrated an association between the presence of antibodies in women with endometriosis and **infertility**. Despite intensive study, there is also no consensus on a role of autoantibodies to the zona pellucida as a cause of **infertility**. Recently, much attention has been focused on autoantibodies and **infertility**, particularly on phospholipid antibodies and their effect on IVF success rates. The published studies suggest that women with **infertility** have an increased prevalence of phospholipid antibodies compared with fertile women. The presence of these antibodies, however, has not been associated with a worsened prognosis for IVF cycles. Many questions remain to be answered. What is the cause of this apparently increased prevalence of autoantibodies in infertile women? Do these autoantibodies cause **infertility**, or are they merely associated with some other condition that is actually causative? Finally, can treatment of autoantibodies improve pregnancy rates in infertile couples after IVF or

other **infertility** treatments? One key factor in immune- directed therapy may be the gestational age at which one starts treatment. It may be that if one waits until after cardiac activity is established before therapy is initiated, this may select a group of patients who have a high probability of having a live birth. Therefore, when designing randomized trials, it may be important to begin therapy as soon as a pregnancy test is positive or at least by 5 weeks' gestation. Immunologic therapy has been directed at both autoimmune and suspected alloimmune-associated pregnancy wastage. Because the maternal-fetal **immune tolerance** that allows for maternal acceptance of embryonic implantation and growth is poorly understood, it also has been difficult to identify tests that can differentiate between alloimmune and nonimmune-associated pregnancy failure. The answers to these questions should be sought by carefully conducted trials with appropriate control groups. Subjecting patients to expensive testing and 'treatments' before these answers are known is not consistent with good scientific or medical practice.

L7 ANSWER 13 OF 57 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2000:36795 Document No.: PREV200000036795. Introduction to immunology and autoimmunity. Smith, Dorinda A.; Germolec, Dori R. [Reprint author]. Research Triangle Park, NC, 27709, USA. Environmental Health Perspectives, (Oct., 1999) Vol. 107, No. SUPPL. 5, pp. 661-665. print.
CODEN: EVHPAZ. ISSN: 0091-6765. Language: English.

AB Autoimmune disease occurs when the immune system attacks self-molecules as a result of a breakdown of immunologic tolerance to autoreactive immune cells. Many autoimmune disorders have been strongly associated with genetic, infectious, and/or environmental predisposing factors. Comprising multiple disorders and symptoms ranging from organ-specific to systemic, autoimmune diseases include insulin-dependent diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, thyroiditis, and multiple sclerosis. There are also implications of autoimmune pathology in such common health problems as arteriosclerosis, inflammatory bowel disease, schizophrenia, and certain types of **infertility**. Largely of unknown etiology, autoimmune disorders affect approximately 3% of the North American and European populations, > 75% of those affected being women. This discussion provides a brief introduction to the immune system and tolerance maintenance, an overview of selected autoimmunediseases and possible mechanisms of immune autoreactivity, and a review of experimental autoimmune models.

L7 ANSWER 14 OF 57 MEDLINE on STN

1999283526. PubMed ID: 10355099. [Maternal anti-paternal reactivity--depends on etiology]. Mutterliche antipaternale Reaktivitat--auf das WIE kommt es an. Schutt C. (Institut fur Immunologie und Transfusionsmedizin, Ernst-Moritz-Arndt-Universitat Greifswald.) Zentralblatt fur Gynakologie, (1999) 121 (4) 202-5. Ref: 10. Journal code: 21820100R. ISSN: 0044-4197. Pub. country: GERMANY: Germany, Federal Republic of. Language: German.

AB Since TH1-cytokines compromise pregnancy and TH2-cytokines are produced at the maternal-fetal interface one can hypothesize that TH2-cytokines improve fetal survival. Cytotoxic T- or NK-cells are unable to recognize MHCI/II-negative trophoblast or become inactivated by HLA-G expression, respectively. Normal delivery at term might be assisted by a rapid reversal of the TH2 cytokine bias. Thus, the maternal immune state is most beneficial to reproductive fitness.

L7 ANSWER 15 OF 57 MEDLINE on STN

97340087. PubMed ID: 9196597. Glycodelins as regulators of early events of reproduction. Seppala M; Koistinen H; Koistinen R; Dell A; Morris H R; Oehninger S; Clark G F. (Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, Finland.) Clinical endocrinology, (1997 Apr) 46 (4) 381-6. Ref: 46. Journal code: 0346653. ISSN: 0300-0664.

Pub. country: ENGLAND: United Kingdom. Language: English.

L7 ANSWER 16 OF 57 MEDLINE on STN

97286129. PubMed ID: 9190356. [Immunological aspects of endometriosis]. Aspectos inmunologicos de la endometriosis. Corchado Gomez A; Hinojosa Cruz J C. (Especialista en Ginecologia y Obstetricia Hospital de Gineco-Pediatria No. 3-A Magdalena de las Salinas, IMSS, Mexico, D.F.) Ginecologia y obstetricia de Mexico, (1997 Mar) 65 79-86. Ref: 34. Journal code: 0376552. ISSN: 0300-9041. Pub. country: Mexico. Language: Spanish.

AB The effect of adherence process on Fallopian tubes and ovaries in late stages endometriosis is clear, but it is more important to understand pathophysiologic mechanism of **infertility** in minimal, mild endometriosis. Although the etiology of endometriosis is unknown, components of the immune system may be involved and play a central role in the pathogenesis of the disease by immunologically altering the peritoneal microenvironment. Increased number and activity of leucocyte subpopulations in the peritoneal fluid result in cytotoxic effects that exert adverse influence on spermatozoa, oocyte, germ cell interaction, and early embryo development, while cytokine and growth factor secretion stimulates or promotes cellular proliferation of endometriotic tissue in an "immunological tolerance" environment. The immunological aspects of endometriosis, including autocrine or paracrine pathways of intercellular communication, are reviewed.

L7 ANSWER 17 OF 57 EMBASE on STN

96288257 EMBASE Document No.: 1996288257. Immunotherapy in neuromuscular disorders: Current and future strategies. Drachman D.B.. Department of Neurology, School of Medicine, Johns Hopkins University, 600 N. Wolfe Street,Baltimore, MD 21287-7519, United States. Muscle and Nerve 19/10 (1239-1251) 1996.
ISSN: 0148-639X. CODEN: MUNEDE. Pub. Country: United States. Language: English. Summary Language: English.

AB Autoimmune mechanisms have recently been implicated in the pathogenesis of an increasing number of neuromuscular diseases. Many of these diseases can be treated with immunotherapeutic agents that are currently available-often with striking success. However, lack of specificity and adverse side effects impose limits on the effectiveness of these immunosuppressive treatments. This article reviews the basic principles of autoimmunity and **immune tolerance**, and outlines strategies that produce (a) generalized immunosuppression; (b) 'selective' immunotherapy; and (c) 'antigen-specific' immunotherapy. General immunosuppressive treatments, which are the ones most commonly used in current practice, down-regulate the immune system at multiple levels in 'shotgun' fashion. The agents described here include: adrenal corticosteroids, azathioprine, cyclophosphamide, chlorambucil, methotrexate, total lymphoid irradiation, plasmapheresis, and intravenous immunoglobulin. 'Selective' immunotherapeutic strategies are designed to interfere with mechanisms intrinsic to the immune system. Agents that are now being used clinically, or are in advanced stages of development include: cyclosporin A, which interferes with synthesis of the cytokine interleukin 2 (IL2); IL2 toxin, which binds to IL2 receptors on activated T cells, is endocytosed, and kills the cells; and CTLA4Ig, which blocks costimulatory molecules, thus preventing full activation of T cells. We have found that combinations of the selective agents may enhance their effectiveness. 'Specific' strategies are designed to inactivate or suppress antigen-specific T cells. Oral administration of autoantigens has been shown to prevent experimental autoimmune diseases specifically, but the conditions required to suppress ongoing autoimmune diseases are capricious, and depend on many factors. Finally, we describe a method that is still in the experimental stage, which is designed to modify the individual's own antigen-presenting cells so that they will target and inactivate antigen-specific T cells, and thereby turn off the specific

autoimmune response. Currently available immunosuppressive methods can now be used successfully to treat many autoimmune neuromuscular diseases, and the application of selective and specific immunotherapeutic strategies promises more precise and effective treatment in the future.

L7 ANSWER 18 OF 57 MEDLINE on STN
97056696. PubMed ID: 8901036. [Immunology of the fetal-maternal relationship]. Inmunologia de la relacion materno fetal. Gonzalez N C; Chairez J A; Cueto S M. (Departamento de Inmunologia Clinica y Alergia, Hospital de Especialidades del Centro Medico Nacional Siglo XXI, Mexico.) Revista alergia Mexico (Tecamachalco, Puebla, Mexico : 1993), (1996 Jan-Feb) 43 (1) 18-22. Ref: 49. Journal code: 9438824. Pub. country: Mexico. Language: Spanish.

AB For the last 40 years it has been considered that during pregnancy fetal antigens are expressed in a different manner in comparison with other grafts. Current data indicates that the acceptance of the fetus by the mother depends on the lack of expression of the polymorphic antigens and the production of hormones that act as immunological suppressors. During pregnancy there exists immunological recognition of the trophoblast antigens, but these antigens are not polymorphic and thus do not permit the identification of cytolytic T and natural killers cells. This structure also produces hormones that contribute to the diminished production and proliferation of T cells. It has been demonstrated that there exists an increase in the production by the trophoblast of complement inhibitors (DAF, CD46) and in the secretion of hormones such as progésterone, alpha-fetoprotein, steroids and prostanglandins. The identification of these immunological factors and mechanisms may be fundamental in the search for treatment regimens for such illnesses as cancer, **infertility**, spontaneous abortions, transplant rejection and graft versus host disease.

L7 ANSWER 19 OF 57 MEDLINE on STN
96142414. PubMed ID: 8545385. [Immunologic tolerance of fetal allograft]. Tolerance immunologique de l'allogreffe foetale. Deneys V; Van Lierde M; De Bruyere M. (Laboratoire d'Immunohematologie, Cliniques Universitaires Saint-Luc, Bruxelles, Belgique.) Presse medicale (Paris, France : 1983), (1995 Nov 18) 24 (35) 1651-7. Ref: 31. Journal code: 8302490. ISSN: 0755-4982. Pub. country: France. Language: French.

AB In mammals, reproduction involves two potentially incompatible mechanisms: viviparity and development of a competent immune system. Thus the maternal and foetal organisms must respond by developing immunologic tolerance. The phenomenon does not involve total immunosuppression, but includes several highly precise processes initiated at conception. It is known that cell- and humour-mediated processes occur but their relative importance remains to be elucidated. Cytokines, especially those mediating T-helper2 cell response appear to play a predominant role in inducing immunologic tolerance to the foetal allograft. A better understanding of these mechanisms could have major implications in the diagnosis and treatment of repeated miscarriage and unexplained **infertility**.

L7 ANSWER 20 OF 57 MEDLINE on STN
95269811. PubMed ID: 7750580. The biologic significance of white blood cells in semen. Wolff H. (Department of Dermatology, Ludwig-Maximilians-University, Munich, Germany.) Fertility and sterility, (1995 Jun) 63 (6) 1143-57. Ref: 202. Journal code: 0372772. ISSN: 0015-0282. Pub. country: United States. Language: English.

AB OBJECTIVE: To analyze the data available on the biologic significance of white blood cells (WBC) in semen of **infertility** patients. DATA RESOURCES: The relevant literature was reviewed. RESULTS: It is not possible to identify reliably WBC by conventional sperm staining techniques. The peroxidase method is sufficient for quantification of granulocytes, but immunocytology is the gold standard for the detection of all WBC populations in semen. Granulocytes are the most prevalent WBC

type in semen (50% to 60%), followed by macrophages (20% to 30%) and T-lymphocytes (2% to 5%). The prevalence of leukocytospermia (> 10(6) WBC/mL semen) among male **infertility** patients is approximately 10% to 20%. There is controversy on the significance of WBC in semen. Whereas some authors did not observe sperm damage in the presence of leukocytospermia, others have found evidence that WBC are significant cofactors of male **infertility**: [1] seminal WBC numbers were higher in **infertility** patients than among fertile men; [2] leukocytospermia was associated with decreased sperm numbers and impaired sperm motility; [3] WBC damaged sperm function and hamster ovum penetration in vitro and were important prognostic factors for IVF-ET failure. Because of absence of clinical symptoms, the origin of WBC is difficult to determine. Normally, most WBC appear to originate from the epididymis because vasectomized men show very few WBC in semen. On the other hand, leukocytospermic samples show low citric acid levels, pointing to asymptomatic prostatitis as a source of WBC in semen. Surprisingly, approximately 80% of leukocytospermic samples are microbiologically negative. In some cases Chlamydia trachomatis might have triggered a persistent inflammatory reaction leading to leukocytospermia. Sperm damage by WBC can be mediated by reactive oxygen species, proteases and cytokines. Furthermore, genital tract inflammation facilitates the formation of sperm antibodies. As seminal plasma has strong anti-inflammatory properties and because there is only short contact between sperm and WBC in prostatitis and seminal vesiculitis, inflammations of the epididymis and testis are likely to have the largest impact on sperm. CONCLUSIONS: There is ample evidence that WBC can affect sperm function. Further studies are needed to define cofactors that increase or decrease the risk of sperm damage by WBC.

L7 ANSWER 21 OF 57 MEDLINE on STN

96269266. PubMed ID: 8700806. [Immunologic reactions in the male and female reproductive system]. Reakcje immunologiczne zachodzace w zenskim i meskim ukladzie rozrodczym. Kasprzak M; Domagala A; Tabor J; Kurpisz M. (Zaklad Genetyki Czlowieka PAN w Poznaniu.) Postepy higieny i medycyny doswiadczalnej, (1995) 49 (6) 693-717. Ref: 47. Journal code: 0421052. ISSN: 0032-5449. Pub. country: Poland. Language: Polish.

AB This review describes presence and significance of antisperm antibodies (ASA) in male and female reproductive compartments. We described their relevance to **infertility** in humans. A structure and function of cervical mucus as the environment of females defensive reactions against all the invasive factors is outlined. There are also briefly characterized techniques of ASA detection.

L7 ANSWER 22 OF 57 MEDLINE on STN

2002556640. PubMed ID: 12319249. [Sperm antibodies and fertility]. Auto-anticorps antispermatozoides et fertilite. Verpillat P; Boiron J; Roux C; Agnani G. Contraception, fertilite, sexualite, (1995 Feb) 23 (2) 87-92. Journal code: 0411244. ISSN: 0301-861X. Report No.: PIP-103704; POP-00239817. Pub. country: France. Language: French.

AB Some cases of **infertility** considered inexplicable have been found to have an immunologic basis. Spermatozoa are highly antigenic cells. When the state of **immune tolerance** is disrupted, auto-immunization in the man or isoimmunization in the woman can occur. The appearance of antibodies directed against the sperm antigens results in a condition of hypofertility more than of absolute sterility. Numerous antigens have been identified on sperm using monoclonal antibodies. Immunosuppressive substances have been isolated in the seminal liquid in vitro, and various other protective mechanisms have been identified. Autoimmunity apparently results from failure of the protective processes. Physical, chemical, or infectious trauma may explain the entry of immunocompetent cells. The most commonly used techniques for study of antisperm antibodies are those that detect antibodies directed against surface antigens. Sperm agglutination tests

have been criticized for their numerous false positive findings and their failure to identify the classes of immunoglobulins implicated. Tests of immobilization or cytotoxicity are specific, with no false positives, but not sensitive, giving rise to false negatives. The Mixed Antiglobulin Reaction Test (MAR- test) is very specific, easy, inexpensive, and rapid, but it only detects IgG and determination of the place of fixation is difficult. The immunobead test proposed in 1982 overcame some of the limitations of the MAR-test. These two are the methods of choice in exploration of male autoimmunity. Radioimmunologic techniques, an ELISA-type test, and others have given less satisfactory results. The frequency of antisperm antibodies has been estimated at 3 to 15% in nonselected infertile men, 35% among men with some symptoms or a history of the condition, and less than 1% among fertile men. The antisperm antibodies have functional significance only when they are fixed to their antigens. Modifications of sperm mobility are the main problem, with blockage of transport to the oocyte and union with it. It is difficult to establish a prognosis because evaluation must be done individually. As the level of antibodies increases, the chances of spontaneous pregnancy decline. Several treatments have been developed but results have been disappointing. In vitro fertilization after separation of motile sperm without antibodies may improve the prospects of pregnancy.

L7 ANSWER 23 OF 57 MEDLINE on STN DUPLICATE 3

94252413. PubMed ID: 8194608. Antisperm antibodies: origin, regulation, and sperm reactivity in human **infertility**. Naz R K; Menge A C. (Department of Obstetrics and Gynecology, Albert Einstein College of Medicine, Bronx, New York 10461.) Fertility and sterility, (1994 Jun) 61 (6) 1001-13. Ref: 82. Journal code: 0372772. ISSN: 0015-0282. Pub. country: United States. Language: English.

AB OBJECTIVE: To follow-up and expand discussion on the action mechanisms of antisperm antibodies in human **infertility**, the etiology and control of antisperm antibody induction, sperm antigens involved in immunoinfertility, and strategies for therapy. DESIGN: A review of the recent literature with an emphasis on female immunoinfertility. RESULTS: The role of antisperm antibodies in clinical **infertility** continues to be defined. Through assisted reproductive technologies, antisperm antibodies were shown to exert detrimental effects on different prefertilization and possibly postfertilization events. The female reproductive tract is part of the common mucosal immune system and is able to mount effective immune responses against infectious agents, foreign antigens, and, occasionally, sperm cells. Sperm membranes and constituents contain numerous antigenic components foreign to the human body, and yet antisperm antibodies become problematic in few women exposed to semen. Semen and sperm cells contain immunosuppressive factors capable of inhibiting different immune cells. Fertile women apparently produce antisperm antibodies but also possess neutralizing serum anti-idiotypic antibodies that are lacking in virgin and immunoinfertile women. CONCLUSIONS: Antisperm antibodies can affect adversely human fertility but normally may be controlled by anti-idiotypic antibodies, which along with immunosuppressor factors in semen prevent their induction to a significant degree. This balance between detrimental and "beneficial" immune response to sperm may be shifted toward an antisperm antibody response by stimulatory factors such as infection. Therapies may be devised to stimulate the anti-idiotypic antibody system, to induce **immune tolerance** to sperm antigens, and to use antigens to adsorb antisperm antibodies from spermatozoa.

L7 ANSWER 24 OF 57 MEDLINE on STN

94177765. PubMed ID: 8131311. Endometriosis: the host response. Grosskinsky C M; Halme J. (University of North Carolina at Chapel Hill 27599.) Bailliere's clinical obstetrics and gynaecology, (1993 Dec) 7 (4) 701-13. Ref: 100. Journal code: 8710782. ISSN: 0950-3552. Pub. country: ENGLAND: United Kingdom. Language: English.

AB There is abundant evidence of altered immune function in endometriosis.

The task that remains is to attempt a synthesis from the accumulated data, to try to make some sense of the observed phenomena and to fit them into a conceptual framework; this might permit the formulation and testing of hypotheses. Evidently, eutopic endometrium does not engender an immune response in normal subjects, otherwise the endometrium would be subject to autoimmune destruction. It has also been established that the overwhelming majority of women regurgitate menstrual debris into the peritoneal cavity. Why does this lead to endometriosis in some, but not in others? There are several possible explanations. The uterus might act as a privileged site, i.e. be exempt from immune effector mechanisms. This would certainly be conducive to the reproductive goal, the survival of the fetal allograft. Endometrium would then not enjoy the immunologic tolerance of most other tissues, and upon leaving the uterus and entering an immunocompetent environment would be subject to immune attack. In normal subjects, this could consist of elimination of menstrual debris without further sequelae. An altered response, characterized by the production of antibody that could mask receptors for cytotoxic or phagocytic effector cells, would permit persistence of ectopic endometrium. The alternative to this hypothesis is that the uterus is not a privileged site, and that the organism is normally tolerant to endometrial antigens. Menstrual debris would be eliminated intraperitoneally without loss of tolerance due to the presence of homeostatic mechanisms including suppressor T cells and suppressive cytokines. In endometriosis, this tolerance breaks down, as is the case in several autoimmune disorders, causing a chronic inflammatory response with the release of toxic factors and, eventually, peritoneal scarring. Finally, the role of cell adhesion molecules, including the integrins, is only just being explored. The behaviour of these molecules in ectopic endometrium differs from that in eutopic endometrium, and it remains to be seen whether regurgitated endometrial debris from normal subjects is different from that of endometriosis sufferers. It seems that this will be an area of intense investigation in the immediate future.

L7 ANSWER 25 OF 57 MEDLINE on STN

94098912. PubMed ID: 8273398. [Immunization with partner lymphocytes: improvement of pregnancy rate in sterility patients]. Immunisierung mit Partner-Lymphozyten: Verbesserung der Schwangerschaftsrate bei Sterilitatspatienten. Kuhn U; Campo R; Hinney B; Neumeyer H; Criel A; Gordts S; Kuhn W. (Abteilung fur Geburtshilfe und Perinatale Medizin, Universitat Essen.) Zeitschrift fur Geburtshilfe und Perinatologie, (1993 Sep-Oct) 197 (5) 209-14. Journal code: 0326205. ISSN: 0300-967X. Pub. country: GERMANY: Germany, Federal Republic of. Language: German.

AB In a two-centre prospective study 20 patients with a history of unsuccessful sterility treatment underwent immunization with paternal lymphocytes to improve the pregnancy rate in the subsequent therapeutic AIH or IVF/ET cycle. Unsuccessful sterility treatment was defined as no pregnancy after 8 properly monitored AIH cycles and at least one diagnostic IVF/ET or more than 3 IVF with transfer of 3 embryos. After successful immunization expressed by the induction of Fc-receptor blocking antibodies 10/20 patients became pregnant. Nine of these patients delivered healthy children, one patient experienced a first trimester abortion. A successful second pregnancy occurred in 6 of these patients. No significant correlation between the previous history and pregnancy success could be found, except a slight advantage for patients with a history other than tubal sterility. There were no differences in the anamnestic data as well as in the success rate between the two independent centres Gottingen and Leuven (10 patients each). These data suggest, that adjuvant immunotherapy might improve markedly the pregnancy rates in selected cases of sterility.

L7 ANSWER 26 OF 57 MEDLINE on STN

94012213. PubMed ID: 8407574. Soluble Fc gamma RIII (CD16) and immunoglobulin G levels in seminal plasma of men with immunological **infertility**. Sedor J; Callahan H J; Perussia B; Lattime E C;

Hirsch I H. (Department of Urology, Jefferson Medical College, Philadelphia, Pennsylvania 19107.) Journal of andrology, (1993 May-Jun) 14 (3) 187-93. Journal code: 8106453. ISSN: 0196-3635. Pub. country: United States. Language: English.

AB Receptors for the Fc region of the immunoglobulin G (IgG) (Fc gamma R) have been recognized as a link between humoral and cellular immune responses. A soluble form of Fc gamma RIII (CD16) has been found in seminal plasma (SP), which may modulate immunosuppression of antisperm immune responses in the male and female reproductive tracts. SP from some individuals apparently have lower levels of Fc gamma RIII, but it is not known whether the diminished activities are due to low receptor concentration or steric interference from IgG. To test the hypothesis that different levels are due to steric interference, relative levels of Fc gamma RIII were measured in SP using monoclonal antibody 3G8 in an amplified enzyme-linked immunosorbent assay (ELISA) system. Men who were positive for antisperm antibodies (ASA) by Sperm Mar and direct immunobead assay (N = 26) and negative for ASA (N = 26) were tested. Individuals who were ASA positive had lower detectable levels than those who were ASA negative (t = 1.99, P = 0.05). Therefore, variation in Fc gamma RIII levels may be due to steric interference from IgG. IgG subclass concentrations in SP of both groups were determined using an ELISA method and compared to Fc gamma RIII levels. Slight correlations were seen for IgG1 (r2 = 0.237, P < 0.001), IgG2 (r2 = 0.204, P < 0.001), and total IgG (r2 = 0.299, P < 0.001) in relation to Fc gamma RIII levels in ASA-negative SP specimens.(ABSTRACT TRUNCATED AT 250 WORDS)

L7 ANSWER 27 OF 57 MEDLINE on STN

94007201. PubMed ID: 8403428. Progesterone immunosuppressive levels and luteal steroid profiles in the cycles induced with clomiphene citrate. Scarpellini F; Scarpellini L; Dino N; Benvenuto P. (II Institute of Obstetrics and Gynaecological, University of Rome, La Sapienza.) Clinical and experimental obstetrics & gynecology, (1993) 20 (3) 182-8. Journal code: 7802110. ISSN: 0390-6663. Pub. country: Italy. Language: English.

AB Several studies have focused their attention on the possible interferences of the endocrine with the immunity system; these interrelations have been summoned to explain some aspects of the implantation. It has already been demonstrated that progesterone could play an immunosuppressive role, allowing the implantation of allotransplantation. However, the individual plasmatic levels of the substance needed to produce that effect still unknown. With the aim of determining the certain immunosuppressive progesterone levels in women with normal ovulatory function, and in order to determine if the other principal steroids might also have immunosuppressive effects, in 47 women affected by sine causa **infertility**, treated with 100 mg. die of Clomiphene Citrate (from day 3 to day 7) we evaluated the plasma levels of progesterone, 17-OH-Progesterone and 17 beta-Estradiol. The assays were made on the 7th, 11th and 14th post-ovulation days both in women who conceived (immunosuppressive effect present) and in women who did not achieve pregnancy (immunosuppressive effect absent). The results achieved showed a significant difference only in the progesterone values, while those of the other steroids were not significantly different, indicating thus that progesterone is the main element responsible for the immunosuppressive phenomenon and that the seriated evaluation in the luteal phase of this steroid could be used as a marker of achieved implantation.

L7 ANSWER 28 OF 57 MEDLINE on STN

92279622. PubMed ID: 1594827. [Immunology of pregnancy]. Immunologie de la grossesse. Gotlieb W H. (Service de Gynecologie, Hopital Erasme, Bruxelles.) Revue medicale de Bruxelles, (1992 Apr) 13 (4) 97-101. Ref: 22. Journal code: 8003474. ISSN: 0035-3639. Pub. country: Belgium. Language: French.

AB The fetus expresses paternally inherited gene products and tissue-specific differentiation antigens. Hence, it can be considered as a semi-allogeneic graft towards which the maternal immune response is

characterized by tolerance instead of rejection. As such, the pregnancy represents a challenge to the laws of transplantation. For the immunologist, the question is not why some women miscarry, but rather, why most women do not miscarry? A bulwark of proscriptive or inhibitory influences must be built to ensure an absence of anti-fetal reactivity. The mechanisms underlying the induction of tolerance are poorly understood. Failure to obtain an adequate maternal immune response might be responsible for some forms of miscarriages, especially recurrent spontaneous abortions. Increased knowledge of those mechanisms could have implications in various fields, such as **infertility**, transplantation and oncology.

L7 ANSWER 29 OF 57 MEDLINE on STN

92255423. PubMed ID: 1580700. Cell mediated immunity in **infertility**. Mallmann P; Diedrich K. (Department of Gynecology and Obstetrics, University of Bonn, FRG.) Archives of gynecology and obstetrics, (1992) 251 (2) 55-63. Ref: 54. Journal code: 8710213. ISSN: 0932-0067. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

L7 ANSWER 30 OF 57 MEDLINE on STN

93077772. PubMed ID: 1280281. Endometrial proteins: a reappraisal. Seppala M; Julkunen M; Riittinen L; Koistinen R. (Department I of Obstetrics and Gynaecology, Helsinki University Central Hospital, Finland.) Human reproduction (Oxford, England), (1992 Jun) 7 Suppl 1 31-8. Ref: 105. Journal code: 8701199. ISSN: 0268-1161. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Uterine factors influence reproduction at the macro-anatomy level, and the effects of hormonal steroids on endometrial morphology are well recognized in the histopathological diagnosis of dysfunctional bleeding and **infertility**. During the past decade, attention has been paid to endometrial protein synthesis and secretion with respect to endocrine stimuli and implantation, and to the paracrine/autocrine effects of endometrial peptide growth factors, their binding proteins and other factors. The emphasis of this presentation is on protein secretion of the secretory endometrium, in which progesterone plays a pivotal role. Insulin-like growth factors have receptors on the endometrium, and IGF-binding proteins, stimulated by progesterone, modulate the effects of IGFs locally. Also other protein products of the secretory endometrium have been reviewed in this communication, with special emphasis on studies of a progesterone-associated endometrial protein which has many names in the literature, such as PEP, PP14, alpha 2-PEG and AUP. Extensive studies are ongoing in many laboratories to elucidate the regulation, function, interplay at tissue and cellular levels, and clinical significance of these proteins.

L7 ANSWER 31 OF 57 MEDLINE on STN

91334528. PubMed ID: 1871176. Immunosuppression by seminal plasma from fertile and infertile men: inhibition of natural killer cell function correlates with seminal PG concentration. Kelly R W; Quayle A J; Wallace E M; Wu F C; Hargreave T B; James K. (MRC Reproductive Biology Unit, University of Edinburgh Centre for Reproductive Biology.) Prostaglandins, leukotrienes, and essential fatty acids, (1991 Apr) 42 (4) 257-60. Journal code: 8802730. ISSN: 0952-3278. Pub. country: SCOTLAND: United Kingdom. Language: English.

AB Human seminal plasma has uniquely high concentrations of PGE and 19-hydroxy PGE but the function of these PGs has not been elucidated. PGs of the E series have been shown to be paracrine and autocrine regulators of the function of immune cells and high levels of PGE have been shown consistently to suppress function in such cells. Human seminal plasma has a potent immunosuppressive effect and evidence is accumulating that this is largely due to PG components. In this study the effects of human seminal plasma on the killing activity of natural killer (NK) cells as judged by 51Cr release from K562 cells have been studied in groups of

fertile and infertile men. Although there was no significant difference in the PGE, 19-hydroxy PGE or the NK cell inhibitory activity in the two groups, the inhibition of NK cell activity was closely correlated with the PGE and the 19-OH PGE content of the seminal plasma in the fertile group. This finding is further evidence that the major contribution to the immunosuppressive properties of human semen is provide by the high concentration of PGs of the E series in this fluid.

L7 ANSWER 32 OF 57 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1991:305613 Document No.: PREV199141014203; BR41:14203. **INFERTILITY** DUE TO ANTI-SPERM ANTIBODIES IN CERVICAL MUCUS ASSOCIATED WITH OCCULT AUTO-IMMUNE DISEASE. FOX R [Reprint author]. UNIV BRISTOL, DEP OBSTETRICS GYNAECOLOGY, BRISTOL MATERNITY HOSP, SOUTHWELL STREET, BRISTOL BS2 8EG, UK. Journal of Obstetrics and Gynaecology (Abingdon), (1991) Vol. 11, No. 2, pp. 152.
CODEN: JOGYDW. ISSN: 0144-3615. Language: ENGLISH.

L7 ANSWER 33 OF 57 MEDLINE on STN

91059924. PubMed ID: 2245843. Analysis of immunosuppressive molecules associated with murine in vitro fertilized embryos. Porat O; Clark D A. (Department of Medicine, McMaster University, Hamilton, Ontario, Canada.) Fertility and sterility, (1990 Dec) 54 (6) 1154-61. Journal code: 0372772. ISSN: 0015-0282. Pub. country: United States. Language: English.

AB Supernatants from mouse in vitro fertilized (IVF) oocyte cultures may suppress in vitro lymphocyte proliferation stimulated by concanavalin A (Sigma, St. Louis, MO). Supernatants conditioned by incubation with mouse epididymal sperm alone were even more inhibitory. Thin-layer chromatography suggested the polyamines spermine in sperm and spermine plus spermidine in IVF embryo supernatants were responsible. Putrescine was not suppressive. In vitro fertilized oocytes from old CBA/J-strain mice (greater than 20 weeks) that suffer age onset **infertility** lacked suppression and manifest cleavage arrest that could be partially reversed by adding spermine to the cultures. The failure of IVF oocytes to produce adequate quantities of polyamines could lead to failure of implantation due to division arrest. A possible in vivo role of polyamines as immunosuppressor factors is discussed.

L7 ANSWER 34 OF 57 MEDLINE on STN

90127480. PubMed ID: 2298311. Immunosuppressive properties of human follicular fluid. Castilla J A; Molina R; Lopez-Nevot M A; Vergara F; Garrido F; Herruzo A J. (Ciudad Sanitaria Virgen de las Nieves, Granada, Spain.) Fertility and sterility, (1990 Feb) 53 (2) 271-5. Journal code: 0372772. ISSN: 0015-0282. Pub. country: United States. Language: English.

AB Human preovulatory follicular fluids (FF) obtained in the course of stimulated cycles were analyzed for their possible immunologic functions. Different concentrations of FF (20%, 2%, 1%) inhibited the mitogenic response of normal human lymphocytes to concanavalin A (Con A). Lymphocytes were assessed for immunosuppressor activity after preincubation with FF. Lymphocyte mitogenic response to Con A was only suppressed by cells preincubated with FF at concentrations of 2% and 1% for at least 48 hours. No evidence of suppressor cell induction was seen following incubation of lymphocytes with 20% FF, nor was any significant relationship between FF immunosuppressor activity and the outcome of in vitro fertilization observed. We conclude that some factor(s) in FF may be capable of directly inhibiting lymphocyte response and inducing immunosuppressor cell activity in vitro.

L7 ANSWER 35 OF 57 MEDLINE on STN

91174557. PubMed ID: 2078059. Cellular sensitization against spermatic and seminal plasma antigens in women after intrauterine insemination. Schroder W; Mallmann P; van der Ven H; Diedrich K; Krebs D. (Department of Obstetrics and Gynecology, University of Bonn, FRG.) Archives of gynecology and obstetrics, (1990) 248 (2) 67-74. Journal code: 8710213.

ISSN: 0932-0067. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Using an indirect lymphokine-assay, the leucocyte-migration-inhibition-test (LMI-test), the cellular sensitization of fertile and infertile patients before and after homologous and heterologous intrauterine insemination (IUI) was investigated. In this assay several preparations of spermatozoa ("washed"-, "swim-up"- and "pellet"-spermatozoa) in different concentrations (1, 5 and 10 x 10(6) sperms/ml culture medium) and seminal plasma were tested as antigen. In all investigated groups a cellular immune response against spermatic antigen was demonstrable and seemed to be dose dependent. In contrast to fertile women who reacted with an enhancement of the macrophage migration for low concentrations the same concentration of antigen induced an inhibition of macrophage migration in fertile patients. For high concentrations of spermatic antigens there was a difference in the intensity of cell-mediated immune response between fertile and infertile women. Since infertile patients demonstrated an increased level of cell-mediated immune response it is possible that **infertility** may be caused by this altered immunological reaction. This response changes after multiple IUI-treatment and that change might be caused by the high concentration of spermatic antigens as there was a difference in the intensity of cell-mediated immune response between fertile and infertile women. Since infertile patients demonstrated an increased level of cell-mediated immune response it is possible that **infertility** may be caused by this altered immunological reaction. This response changes after multiple IUI-treatment and that change might be caused by the high concentration of spermatozoa. The immunological response of infertile patients seems to be similar in those receiving husband and donor IUI.

L7 ANSWER 36 OF 57 MEDLINE on STN DUPLICATE 4

90292257. PubMed ID: 2141578. Secretory immune system of the female reproductive tract. II. Local immune system in normal and infected fallopian tube. Kutteh W H; Blackwell R E; Gore H; Kutteh C C; Carr B R; Mestecky J. (University of Alabama Medical Center, Birmingham.) Fertility and sterility, (1990 Jul) 54 (1) 51-5. Journal code: 0372772. ISSN: 0015-0282. Pub. country: United States. Language: English.

AB The existence of a secretory immune system in the female genital tract has been demonstrated by the predominance of immunoglobulin (Ig)A-producing plasma cells in human fallopian tube, uterine cervix, and vagina. Epithelium lining fallopian tubes expresses a receptor for IgA, secretory component (SC), and thus resembles other secretory tissues such as intestine, mammary, lacrimal, and salivary glands. The present study extends the characterization of the local immune system in the fallopian tube and assesses its response to infection. We examined normal and infected fallopian tubes from surgical specimens, obtained at tubal ligation and abdominal hysterectomy, for the presence of Ig-producing cells, T cells, and natural killer cells. All tubular segments contained a predominance of IgA plasma cells in the subepithelial lamina propria. The epithelial cells were strongly positive for SC. Luminal contents stained positively for IgA, SC, and J chain, suggesting that this material contained secretory IgA. Submucosal plasma cells of IgM and IgG classes were less frequent than IgA. T cells were present in numbers approximately twofold greater than plasma cells in normal fallopian tubes. T-suppressor (CD8+) cells, which may function in the induction of **immune tolerance**, were present in the intraepithelial spaces. Infected segments of fallopian tubes demonstrated six- to tenfold increased numbers of plasma cells of all classes. These data suggest that a local immune system is functioning in the human fallopian tube and may provide a first line of defense against tubal infection and the prevention of tubal factor **infertility**.

L7 ANSWER 37 OF 57 MEDLINE on STN

89270663. PubMed ID: 2658605. Failure of sperm-induced immunosuppression: association with antisperm antibodies in women. Witkin S S. (Department of

Obstetrics and Gynecology, Cornell University Medical College, New York, NY 10021.) American journal of obstetrics and gynecology, (1989 May) 160 (5 Pt 1) 1166-8. Journal code: 0370476. ISSN: 0002-9378. Pub. country: United States. Language: English.

AB The ability of husbands' sperm to inhibit proliferation of their wives' lymphocytes was measured. Seventeen of 27 sperm samples tested (63%) inhibited lymphocytes from responding to Candida antigens. Eleven of the 27 women (41%) had sera that were positive for antisperm antibodies; sperm from only four of their husbands (36%) were immunosuppressive. In contrast, 13 of the 16 women (81%) without antisperm antibodies had partners with suppressive sperm. Lymphocytes from four women with antisperm antibodies were inhibited by sperm from a fertile donor although not inhibited by their husband's sperm, whereas in three other antibody-positive women neither the husbands' nor donors' sperm were inhibitory. Antisperm antibodies in some women may arise as a consequence of a failure of sperm from their male partners to inhibit lymphocyte activation.

L7 ANSWER 38 OF 57 MEDLINE on STN

90027288. PubMed ID: 2679748. Immunological aspects of the reproductive organs and implications of intercourse. Anderson D J; Hill J A. (Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.) Current opinion in immunology, (1989 Aug) 1 (6) 1119-24. Ref: 26. Journal code: 8900118. ISSN: 0952-7915. Pub. country: United States. Language: English.

L7 ANSWER 39 OF 57 MEDLINE on STN

89254070. PubMed ID: 2722259. Human seminal plasma suppresses delayed-type hypersensitivity responses to intravaginally deposited sheep red blood cells and sperm: separation of immunosuppressive factors. Lee H K; Ha T Y. (Department of Microbiology and Immunology, Chonbuk National University Medical School, Chonju, Republic of Korea.) International archives of allergy and applied immunology, (1989) 88 (4) 412-9. Journal code: 0404561. ISSN: 0020-5915. Pub. country: Switzerland. Language: English.

AB Although significant progress has been made in identifying the immunosuppressive factors in seminal plasma (SP) and their possible action in vitro, the potential role of SP in naturally occurring normal immune responses in vivo is less certain. Human SP or its fractions, administered 5 or 10 times at 3-day intervals into the mouse vagina simultaneously with washed human sperm or sheep red blood cells, suppressed the delayed-type hypersensitivity reactions to footpad injection of the antigens. However, SP failed to suppress antibody formation to these antigens in the applied experimental conditions. In an in vitro study, SP suppressed the proliferation of human peripheral blood mononuclear cells to phytohemagglutinin. This suppression of in vitro proliferation by SP was mediated by materials of both low (LMW) and high molecular weight (HMW). Among the HMW materials, a factor with approximately 1,500 kilodaltons, partially purified by DEAE-cellulose chromatography and gel filtration, exhibited the most potent suppressor activity in vitro and in vivo. The suppressive activities of SP or its fractions were not abolished by treatment with both heat (95 degrees C for 10 min) and trypsin (1.0 mg/ml, 37 degrees C for 4 h). These findings indicate that SP could contribute to the development of suppressed cellular immunity to sperm; immunosuppressive actions of SP are mediated by at least two distinct factors in vivo as well as in vitro.

L7 ANSWER 40 OF 57 MEDLINE on STN

89362244. PubMed ID: 2769648. Association between recurrent spontaneous abortions and circulating IgG antibodies to sperm tails in women. Witkin S S; Chaudhry A. (Department of Obstetrics and Gynecology, Cornell University Medical College, New York, New York 10021.) Journal of reproductive immunology, (1989 May) 15 (2) 151-8. Journal code: 8001906. ISSN: 0165-0378. Pub. country: Netherlands. Language: English.

AB The isotype and regional specificity of antisperm antibodies in the

circulation of women with recurrent spontaneous abortions was examined. There was a statistically significant association (P less than 0.005) between the presence of IgG tail-directed antisperm antibodies and a history of unexplained recurrent spontaneous abortion. These antibodies were detected in 36.4% of 44 women with recurrent abortions and 14.6% of 616 female partners of infertile marriages. In contrast, no differences in IgG sperm head-directed antibodies or in IgA and IgM antisperm antibodies were observed between the two groups. Husbands of women in the miscarriage or infertile groups had similar semen evaluations. Antisperm antibodies may be a marker for defective immunosuppression in women with recurrent miscarriages. Alternatively, exposure of sperm-sensitized pregnant women to sperm may activate the maternal immune system to respond to paternal antigens present on the embryo.

L7 ANSWER 41 OF 57 MEDLINE on STN

89172400. PubMed ID: 3234941. [Immunologic diagnosis in normal pregnancy and idiopathic abortion]. Immunologische Diagnostik bei normaler Schwangerschaft und beim idiopathischem Abort. Flores-Genger H; Schwartz D; Hajek-Rosenmayr A; Huber J C. Gynakologische Rundschau, (1988) 28 Suppl 2 56-7. Journal code: 0011363. ISSN: 0017-6001. Pub. country: Switzerland. Language: German.

L7 ANSWER 42 OF 57 MEDLINE on STN

88036400. PubMed ID: 3312681. Reproductive immunology. Gurka G; Rocklin R E. JAMA : journal of the American Medical Association, (1987 Nov 27) 258 (20) 2983-7. Ref: 27. Journal code: 7501160. ISSN: 0098-7484. Pub. country: United States. Language: English.

AB The maternal immune system is challenged with paternal antigens through exposure to trophoblast tissue and fetal cells crossing the placenta into the maternal circulation. The dose of antigen, the manner of presentation (cellular, subcellular, or soluble), and the nature of the antigen all determine the type of response that will be elicited. It is also clear that complex maternal immunologic responses, including antibodies to red blood cell antigens, HLA-A, HLA-B, HLA-C, and HLA-D antigens, and cell-mediated responses such as proliferation, lymphokines, cytotoxicity, and suppressor cells, are generated to a variety of paternal antigenic determinants. The fact that some of these reactions are detected in vitro in the absence of maternal serum, but not in its presence, suggests that the local milieu is important in influencing their expression in vivo. For example, such factors as hormones (cortisol, progesterone, and estrogen), pregnancy-associated glycoproteins (alpha 2-macroglobulin and beta 1-glycoprotein) and AFP, which have immunosuppressive properties, may all serve nonspecifically to inhibit and decrease the general tone of maternal immunologic responses, particularly at the placental interface, where many of these factors are present in high concentrations. However, these nonspecific factors may not be sufficient to prevent presensitized effector lymphocytes from continuing an ongoing rejection process, as is often the case in the chronic rejection of an allograft. For this purpose, specific enhancing antibodies would play an important role by blocking maternal responses or protecting the fetus. There may be a subtle balance created on the trophoblast cell surface between specific antibodies and trophoblast or embryonic alloantigens, resulting in limited expression of antigens capable of inducing rejection reactions. This could favor the production of blocking antibodies and/or T-suppressor cells, as opposed to cytotoxic antibody and killer cells. In fact, low levels of antigen density on the cell surface favor a blocking effect by IgG rather than cytotoxicity. Blocking or enhancing antibodies can exert their effect on maternal immunologic responses in several ways. They could block the afferent limb by combining with antigen and preventing sensitization or increasing the level of sensitivity. An example of the latter would be the coating of fetal cells that enter the maternal circulation. Enhancing antibodies could work directly on the effector cells to suppress their function. The antibody itself, or more likely antigen-antibody complexes, may be important in this regard. (ABSTRACT

TRUNCATED AT 400 WORDS)

L7 ANSWER 43 OF 57 MEDLINE on STN
87293494. PubMed ID: 3303599. New areas of research in male **infertility**. Mellinger B; Goldstein M. Urologic clinics of North America, (1987 Aug) 14 (3) 619-32. Ref: 111. Journal code: 0423221. ISSN: 0094-0143. Pub. country: United States. Language: English.
AB Recent research in male reproduction holds much promise for future clinical application. Research on the relationship between sperm, semen, and the immune system may provide novel approaches to treating immune-related **infertility**. Investigations of sperm motility have shed new light on these complex mechanisms and may lead to rational approaches to the improvement of sperm function. New assays for secretory products unique to the testis show potential as markers for specific testicular cellular functions. In-vitro fertilization promises to become a viable treatment option for couples with male-factor **infertility** . Research on male contraception may lead to the development of safe and reversible male contraceptives.

L7 ANSWER 44 OF 57 MEDLINE on STN
88108499. PubMed ID: 3427343. Studies on the immunosuppressive effect of seminal plasma. Quayle A J; Szymaniec S; Hargreave T B; James K. (University Department of Surgery/Urology, Western General Hospital, Edinburgh.) British journal of urology, (1987 Dec) 60 (6) 578-82. Journal code: 15740090R. ISSN: 0007-1331. Pub. country: ENGLAND: United Kingdom. Language: English.
AB In vitro suppression of immune responses by seminal plasma is well documented, but the mechanism by which it exerts its effects remains to be established. Our studies on T-lymphocyte proliferation and natural killer cell target-cell lysis reveal that seminal plasma mediated suppression is dose-dependent and temperature-dependent, and that cells which have been activated are less susceptible to suppression. In the case of mitogen-induced T-cell responses this results in a decrease in the expression of the Interleukin-2 receptor whose generation is essential to T-cell proliferation. These studies provide further evidence about suppression of the immune response by seminal plasma. This may be a contributory factor in the aetiology of AIDS, other sexually transmitted diseases, **infertility** and malignancies of the urogenital tract including carcinoma of the cervix.

L7 ANSWER 45 OF 57 MEDLINE on STN
87134304. PubMed ID: 2434363. Immunology of semen. Alexander N J; Anderson D J. Fertility and sterility, (1987 Feb) 47 (2) 192-205. Ref: 122. Journal code: 0372772. ISSN: 0015-0282. Pub. country: United States. Language: English.

L7 ANSWER 46 OF 57 MEDLINE on STN
87220060. PubMed ID: 3583090. Immunosuppressant material in human seminal fluid. Inhibition of blast transformation and of NK activity by seminal fluid patients of a male **infertility** clinic. Marcus Z H; Lunenfeld B; Weissenberg R; Lewin L M. Gynecologic and obstetric investigation, (1987) 23 (1) 54-9. Journal code: 7900587. ISSN: 0378-7346. Pub. country: Switzerland. Language: English.
AB Human seminal plasma from normal or patients with abnormal parameters of the ejaculates contains an inhibitory material that expresses potent in vitro inhibitory activity on PHA-M-induced blast transformation and NK activity. Using the test of inhibition of NK activity, the semen samples from individuals with higher concentrations of fructose had higher inhibitory activity. The results described herein suggest that inhibitory activity for blast transformation may be present in the prostatic fluid while the NK inhibition aspects are correlated with the vesicle-marker (fructose). Inhibition of the immune responses by human seminal plasma of the effector functions indicates the interesting implication that soluble factors may indirectly protect against or promote human autoimmune

infertility disease.

L7 ANSWER 47 OF 57 MEDLINE on STN
87112664. PubMed ID: 3543373. Immunosuppression and sperm antibody formation in men with prostatitis. Witkin S S; Zelikovsky G. Journal of clinical & laboratory immunology, (1986 Sep) 21 (1) 7-10. Journal code: 7808987. ISSN: 0141-2760. Pub. country: Italy. Language: English.
AB 16 men with chronic prostatitis were evaluated immunologically in order to examine possible relationships between prostate infection, defective cellular immune responses and the occurrence of sperm antibodies. Peripheral blood mononuclear cells (PBMN) from 14 of 16 (88%) patients exhibited reduced or absent responses in vitro when incubated with an extract of Candida albicans. PBMN proliferation in response to the mitogen Concanavalin A (Con A) was reduced in 5 of 16 (31%) men. In addition, sera from 6 patients inhibited the Candida-induced proliferative response of control PBMC; 2 of these sera also reduced the Con A-directed response. Sperm antibodies, evaluated by an enzyme-linked immunosorbent assay (ELISA) using fresh motile spermatozoa, were found in 9 of 16 (56%) patients. PBMC responses were reduced in all, and suppressive sera present in 5, of the men with sperm antibodies. IgG antibodies predominated. 4 of the sera positive by ELISA also agglutinated spermatozoa. Levels of IgG sperm antibodies were correlated with the degree of immunosuppression by patient sera (p less than 0.02). These data suggest that decreased cellular immunity and enhanced humoral reactivity to sperm are common in men with chronic prostatitis. Both may contribute to an increased rate of prostatic infection in these men.

L7 ANSWER 48 OF 57 MEDLINE on STN
85290656. PubMed ID: 2411785. [Reproduction and immune factors in the male]. Reproduction et facteurs immunitaires chez l'homme. Martin-du-Pan R C; Bischof P; Bourrit B. Journal de gynecologie, obstetrique et biologie de la reproduction, (1985) 14 (3) 285-9. Journal code: 0322206. ISSN: 0368-2315. Pub. country: France. Language: French.
AB Sperm antigenicity is demonstrated by the formation of sperm antibodies following vasectomy and by the possible occurrence of hypersensitivity reactions in women to seminal fluid. It may be that immunosuppressor factors in seminal plasma, as well as certain placental hormones, could explain the fact that sperm are not rejected immunologically in the female genital tract. The role of these different immune factors in male **infertility** and in the pathogenesis of AIDS is discussed.

L7 ANSWER 49 OF 57 MEDLINE on STN
85074574. PubMed ID: 6509587. [The immune system and cell proliferation, fetal tolerance and tumor growth. II]. Imunitni system a tkanova proliferace, tolerance plodu a nadorovy rust. II. Bukovsky A; Presl J. Ceskoslovenska gynekologie, (1984 Nov) 49 (9) 674-5. Journal code: 0042671. ISSN: 0374-6852. Pub. country: Czechoslovakia. Language: Czech.

L7 ANSWER 50 OF 57 MEDLINE on STN
85094740. PubMed ID: 6517180. Anticomplementary activity in human semen and its possible importance in reproduction. Price R J; Roberts T K; Green D; Boettcher B. American journal of reproductive immunology : AJRI : official journal of the American Society for the Immunology of Reproduction and the International Coordination Committee for Immunology of Reproduction, (1984 Oct-Nov) 6 (3) 92-8. Journal code: 8111069. ISSN: 0271-7352. Pub. country: United States. Language: English.
AB We demonstrated anticomplementary activity on once-washed human sperm, and in normal and vasectomized seminal plasmas. It was demonstrated to be a normal component of human semen. The origin of the activity is proposed to be the seminal plasma with sperm adsorption of activity. The properties of the seminal anticomplementary factor were characterized further, and the molecular size was shown to be less than 3500 daltons. Reduced anticomplementary activity was found to be associated significantly with abnormal semen profiles and **infertility** in

males. The activity in seminal plasma was shown to have no effect on complement-dependent sperm immobilizing antibodies in the serum of an infertile woman, implicating an effect on the post-C3 components of the complement pathway. The inhibition of complement-dependent haemolysis and the lack of inhibition of complement-dependent sperm immobilization by the anticomplementary factor are considered in the implications of the role of seminal anticomplementary activity in reproduction.

L7 ANSWER 51 OF 57 MEDLINE on STN
85067684. PubMed ID: 6334406. [Local immunoregulation in sterile men with antispermal autoimmunity]. O mestnoi immunoreguliatsii u bol'nykh, stradaiushchikh besplodiem s antispermal'nym autoimmunitete. Chernyshov V P; Veropotvelian P N; Zavgorodniaia L I; Kravtsova O M. Vrachebnoe delo, (1984 Sep) (9) 65-7. Journal code: 0413607. ISSN: 0049-6804. Pub. country: USSR. Language: Russian.

L7 ANSWER 52 OF 57 MEDLINE on STN
82082764. PubMed ID: 7031700. Etiology of immune **infertility**. Prakash C. Progress in clinical and biological research, (1981) 70 403-12. Ref: 60. Journal code: 7605701. ISSN: 0361-7742. Pub. country: United States. Language: English.
AB Semen of mammalian species contains a built-in system to prevent immunologic sensitization of females against antigens of sperm and seminal plasma in spite of repeated coitus. This prevention of sensitization is likely to be due to the presence of a potent immune response inhibitor originating from one of the sex accessory glands of the male. The inhibitor has been only biologically characterized so far. Failure of this built-in system in the male results in immune response to seminal antigens in the female. This seminal immunity, when of the right kind and magnitude, results in clinical immune-fertility.

L7 ANSWER 53 OF 57 MEDLINE on STN
81074720. PubMed ID: 6969358. Studies on immune **infertility**: a hypothesis on the etiology of immune **infertility** based on the biological role of seminal plasma immune response inhibitor. Prakash C; Lang R W. Mount Sinai journal of medicine, New York, (1980 Sep-Oct) 47 (5) 491-510. Journal code: 0241032. ISSN: 0027-2507. Pub. country: United States. Language: English.

L7 ANSWER 54 OF 57 MEDLINE on STN
81132109. PubMed ID: 7469383. Immunology of reproduction: present trends. Billingham R E; Head J R. Annales d'immunologie, (1980 Sep-Oct) 131D (2) 125-36. Journal code: 0353045. ISSN: 0300-4910. Pub. country: France. Language: English.
AB Over the past decade has come general recognition that, directly or indirectly, immunology intrudes into nearly every aspect of mammalian reproduction. Charles Darwin's notion that the profligacy of women led to reduced fertility gained plausibility with the subsequent discovery of the auto- and alloantigenicity of spermatozoa and of testicular material. From this observation arose the reasonable expectation that immunological control of fertility may be feasible. Discovery of the importance of natural transfer of immunity from mother to offspring, the ontogeny of the immune response and recognition that pregnancy is an almost consistently successful violation of the "laws of transplantation" are only a few highlights or components of the burgeoning, multifaceted field we have come to recognize as the immunology of reproduction. An overview of this subject will be presented with regard to its evolutionary origins, its accomplishments, its current trends and some of its potentialities. The immunology of reproduction has not developed in isolation; in recent years it has benefited enormously from developments in other fields, and in its turn it has exerted its own impact on other disciplines, especially on transplantation. The present preoccupation of many immunologists with immunoregulation stems largely from independent discoveries in the realm of reproductive immunobiology: the etiology of Rh disease and its

prophylaxis, and the principle of immunological tolerance, from investigations on the peculiarities of dizygotic twins in cattle.

L7 ANSWER 55 OF 57 MEDLINE on STN
76247928. PubMed ID: 941392. [Current problems in the immunology of reproduction]. Suvremenni problemi na imunologiia na razmnozhavaneto. Bratanov K. Veterinarno-meditsinski nauki, (1976) 13 (3) 3-7. Journal code: 0414760. ISSN: 0324-1068. Pub. country: Bulgaria. Language: Bulgarian.

L7 ANSWER 56 OF 57 MEDLINE on STN
75143350. PubMed ID: 1079106. Immunological approaches to fertility control. Anonymous. Acta endocrinologica. Supplementum, (1975) 194 3-487. Journal code: 0370313. ISSN: 0300-9750. Pub. country: Denmark. Language: English.

L7 ANSWER 57 OF 57 MEDLINE on STN
69200956. PubMed ID: 5819068. **Infertility** of mice induced by antibodies specific for human chorionic gonadotrophin. Schlumberger H D; Anderer F A. Acta endocrinologica, (1969 Apr) 60 (4) 681-8. Journal code: 0370312. ISSN: 0001-5598. Pub. country: Denmark. Language: English.

=> s l1 and TGF beta
L8 653 L1 AND TGF BETA

=> s l8 and miscarriage
L9 0 L8 AND MISCARRIAGE

=> s l8 and spontaneous abortion
L10 2 L8 AND SPONTANEOUS ABORTION

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L11 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN
2001:807765 Document No. 137:61707 Effect of CD86 costimulation on modulation of Th1/Th2 cytokines expression at maternal-fetal interface. Zhu, Xiaoyong; Li, Dajin; Sun, Xiaoxi; Yan, Yuanchang (Institute of Obstetric & Gynecology, Fudan University, Shanghai, 200011, Peop. Rep. China). Zhongguo Mianyixue Zazhi, 17(9), 483-488 (Chinese) 2001. CODEN: ZMZAEE. ISSN: 1000-484X. Publisher: Zhongguo Mianyixue Zazhi Bianjibu.
AB The role of CD86 costimulation on the modulation of Th1/Th2 cytokines expression at maternal-fetal interface was studied. The abortion-prone CBAxDBA/2 matings were established as the models of **spontaneous abortion** and the nonabortion-prone CBAxBalb/c matings were used as the models of normal pregnancy. The pregnant CBA females were injected i.p. by rat IgG at day 4, 6, 8, 10 of gestation as control. In another two groups, the pregnant CBA females were injected with rat anti-mouse CD86 mAb at day 4, 6, 8, 10 of gestation or injected only once at day 4 of gestation. The embryo resorbing rate was counted at day 14 of gestation. Expression of Th1/Th2 cytokines at the maternal-fetal interface at day 9 and day 14 of gestation was determined by ELISA. In the model of normal pregnancy, the expression of IL-4, IL-10, **TGF-.beta.**2, IFN-γ and TNF-α at day 9 and day 14 had not changed significantly after the blockade of CD86 costimulation, neither did the resorbing rates. While in the model of abortion-prone, the expression of IL 4,IL-10 and **TGF-.beta.**2 in creased, but the expression of IFN-γ and TNF-α declined. Therefore, the resorbing rates decreased significantly. The disorder in the regulation of CD86 costimulation at the maternal-fetal interface may be the important

pathogenic factor that may trigger the rejection of fetus. Blocking the CD86 costimulation at the early stage of pregnancy could recover the physiol. balance of Th1/Th2 at maternal-fetal interface and inducing the maternal-fetal **immune tolerance**.

L11 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN
2001:687850 Document No. 136:245923 Does successful allopregnancy mimic transplantation tolerance?. Gorczynski, Reginald M.; Yu, Gary; Clark, David A. (RM CCRW-2-855, Toronto Hospital; Toronto, ON, M5G2C4, Can.). Graft (Thousand Oaks, CA, United States), 4(5), 338-345 (English) 2001. CODEN: GTOCA5. ISSN: 1522-1628. Publisher: Sage Science Press.
AB A review. The dendritic-cell associated mol. CD200 is up-regulated in rodent transplantation models where successful inhibition of rejection is accomplished. The mechanism by which CD200 achieves this effect involves signaling a receptor, CD200r, on macrophages and/or γδTCR+ cells, both of which have been implicated in adoptive transfer of tolerance. In addition to inhibition of rejection, increased expression of CD200 is associated with altered polarization in cytokine production, with increased expression of IL-4, IL-10 and **TGF.beta.**, and decreased IL-2, IFNγ and TNF-α. Inhibition of rejection can thus be adoptively transferred by IL-10/**TGF.beta.** and a CD200 immunoadhesin and in turn can be inhibited by neutralizing these cytokines or by functional blockade of CD200 expression. Successful pregnancy in allopregnant mice can also be viewed as dependent upon control of graft rejection. Proinflammatory Th1 cytokines (TNF-α + IFN-γ + IL-1) can cause **spontaneous abortion** in mice by a mechanism which involves a novel prothrombinase, fgl2, which promotes fibrin deposition. However, we found that **spontaneous abortion** rates in abortion-prone CBA + DBA/2 matings and in low abortion rate CBA + BALB/c matings were lower than the frequency of implantation sites showing fibrinhi + fgl2 mRNAhi. CD200 expression was present in the same sites as fgl2 mRNA, and neutralization of this CD200 expression by anti-CD200 antibody raised the abortion rate to predicted levels. Conversely, a CD200 immunoadhesin dramatically reduced the abortion rate. We hypothesize that in addition to its role in organ and tissue allograft rejection, CD200 expression is involved in the prevention of **spontaneous abortion** triggered by cytokine up-regulation of fgl2 at the feto-maternal interface.

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=> s l8 and preeclampsia
L12           0 L8 AND PREECLAMPSIA

=> s l1 and preeclampsia
L13          46 L1 AND PREECLAMPSIA

=> s l13 and treatment
L14           3 L13 AND TREATMENT

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L15 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
2004:610096 Document No. 141:156082 Methods for use of Notch signaling for modulation of cytokine production in T cells and therapeutic uses thereof. Champion, Brian Robert; Young, Lesley Lynn; McKenzie, Grahame James (Lorantis Limited, UK). PCT Int. Appl. WO 2004062686 A2 20040729, 149 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GH, GM, HR, HR, HU, HU, ID, IL, IN,

IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB21 20040109. PRIORITY: GB 2003-428 20030109.

AB The invention provides methods for use of modulators of Notch signaling to regulate interleukin 4 expression and T cell immune responses. The invention further claims use of the methods for immunotherapy, to modify the TH1/TH2 balance of an immune response in favor of a TH2 response, by **treatment** of patient's cells in vivo or ex vivo. In the examples of the invention, a fusion protein comprising the extracellular domain of human Delta1 ligand fused to the Fc domain of human IgG4 was immobilized in microtiter plates via its Fc domain. CD4-pos. cell were cultured in the presence of the above fusion protein, stimulated with anti-CD28 antibody, and analyzed for cDNA expression by PCR. The CD4+ cells were restimulated in various ways and the cytokines IL-10 and interferon-γ were measured. Notch ligand signaling was also measured using a luciferase reporter construct in CHO cells cocultured with recombinant CHO cells expressing Delta1 ligand on the surface. Cytokine production was measured in stimulated mouse CD4+ cells under polarizing conditions. Transcription factor and cytokine expression by anti-CD3/28 activated mouse T cells activated under neutral, Th1, or Th2 culture conditions was measured with or without Delta1 protein.

L15 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN

1999:566216 Document No. 131:183879 HLA linked pre-eclampsia and miscarriage susceptibility gene. O'Brien, Margaret; Bermingham, John; Quane, Kathleen A.; Jenkins, David M.; McCarthy, Tommie V. (National University of Ireland, Ire.). PCT Int. Appl. WO 9943851 A1 19990902, 79 pp. DESIGNATED STATES: W: AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-IE12 19990225. PRIORITY: IE 1998-134 19980225; IE 1998-668 19980812.

AB The invention relates to the identification of a susceptibility gene for pre-eclampsia and eclampsia and provides methods and diagnostic kits for diagnosing susceptibility to normal pregnancy, pre-eclampsia, eclampsia, intrauterine growth retardation, miscarriage, or miscarriage-related infertility. The invention is based on analyzing HLA-G or HLA-G linked nucleic acid, or HLA-G protein or HLA-G mRNA or cells or mols. whose concentration changes as a result of HLA-G action. PCR primers are provided for diagnostic detection of polymorphisms at codon-93 and a insertion/deletion in exon 8 of the HLA-G gene. The invention also provides pharmaceutical compns. for and methods of **treatment** of the above conditions.

L15 ANSWER 3 OF 3 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

97032648 EMBASE Document No.: 1997032648. Specific **immune tolerance** during pregnancy after renal transplantation. Fischer T.; Schobel H.; Barenbrock M.. T. Fischer, Department of Gynecology/Obstetrics, University of Erlangen/Nuremberg, Universitaets Str. 21, D-91054 Erlangen, Germany. European Journal of Obstetrics Gynecology and Reproductive Biology 70/2 (217-219) 1996.
Refs: 21.
ISSN: 0301-2115. CODEN: EOGRAL.
Publisher Ident.: S 0301-2115(95)02581-X. Pub. Country: Ireland. Language: English. Summary Language: English.

AB Pregnancy is associated with specific immunological tolerance to fetal antigens suggesting that immunoregulatory processes during pregnancy can induce specific immunological unresponsiveness. We report a case of a female renal transplant recipient who stopped immunosuppressive therapy

during first pregnancy. Despite histologically proven acute renal allograft rejection during the early course of transplantation, no immunological response was observed for 9 years after withdrawal of immunosuppression. Two further pregnancies within that time period did not evoke any renal complications, but were complicated by premature rupture of the amnion and by the development of **preeclampsia**. To our knowledge, there are no reports of such a long-term specific unresponsiveness to a renal allograft without immunosuppressive therapy. Natural and active immunoregulatory mechanism can be related for the development of specific **immune tolerance** to renal allograft in this case.

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L16 0 L1 AND EARLY EMBRYONIC LOSS

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L17 6 L1 AND IMPLANTATION FAILURE

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L18 4 DUP REMOVE L17 (2 DUPLICATES REMOVED)

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L18 ANSWER 1 OF 4 MEDLINE on STN DUPLICATE 1
2001385132. PubMed ID: 11437632. The role of semen in induction of maternal **immune tolerance** to pregnancy. Robertson S A; Sharkey D J. (Reproductive Medicine Unit and Department of Obstetrics and Gynaecology, Adelaide University, Adelaide, SA 5005, Australia.. sarah.robertson@adelaide.edu.au) . Seminars in immunology, (2001 Aug) 13 (4) 243-54. Ref: 94. Journal code: 9009458. ISSN: 1044-5323. Pub. country: United States. Language: English.

AB Successful pregnancy requires a state of maternal **immune** ' **tolerance**' to accommodate antigens expressed by the conceptus. **Implantation failure** and placental pathologies largely reflect insufficiencies in maternal immune adaptation, but progress in devising therapeutic strategies to treat these conditions is stalled because the mechanisms underlying the induction and maintenance of maternal tolerance are unknown. Increasingly, clinical and experimental data support the proposal that insemination has consequences for the reproductive process beyond delivery of male gametes. An emerging hypothesis, based mainly on clinical observations and experiments in mice, is that insemination is causally linked to the activation and expansion of populations of lymphocytes mediating forms of 'active' **immune tolerance** in the implantation site. This review examines existing evidence for a role for semen in the immunology of pregnancy, highlighting the limitations of our existing knowledge and the prospects for future research and its clinical application.

L18 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
1998:760887 Document No. 130:166975 Role of cytokine regulation in pregnancy. Chaouat, G.; Menu, E.; Desmedt, D.; Delage, G.; Martal, J.; Raghupathy, R.; Frydman, R. (Inserm CJF 92-09. Maternite Hospital A Beclere, Clamart, 92140, Fr.). Immunomodulation, 56-69. Editor(s): Upadhyay, Shakti N. Narosa: New Delhi, India. (English) 1997. CODEN: 67AAAN.

AB Studies are cited that indicate that in some cases, repeated **implantation failures** after successful IVF (in vitro fertilization) could be due to a LIF (leukemia inhibitory factor) deficiency. Other studies show that low mol. weight placental suppressor factor induces T cell anergy; that allopregnancy is a TH2 phenomenon; and that TNF levels rise sharply during early parturition onset and their

response to RU 486-induced labor. Other studies on the effects of hormones and hormone receptors on activated lymphocytes in relation to pregnancy are reviewed.

L18 ANSWER 3 OF 4 MEDLINE on STN
89215508. PubMed ID: 2708872. Lack of correlation of immunosuppressive activity secreted by human in vitro fertilized (IVF) ova with successful pregnancy. Armstrong D T; Chaouat G; Guichard A; Cedard L; Andreu G; Denver L. (U.262 INSERM, Paris, France.) Journal of in vitro fertilization and embryo transfer : IVF, (1989 Feb) 6 (1) 15-21. Journal code: 8412594. ISSN: 0740-7769. Pub. country: United States. Language: English.
AB The high rate of **implantation failure** in humans following in vitro fertilization (IVF) has been attributed to a lack of production of immunosuppressive factors by cleaved embryos, rendering them vulnerable to maternal immune attack just before or around implantation. Systemic as well as blastocyst-secreted suppressor factors have been described and claimed to be responsible for successful pregnancy. Experimentally, we have screened in a double-blind fashion the suppressive activity of human embryo culture media (B2 Menezo system, France) in which zygotes after decoronization were individually cultured during 24 hr on lymphocyte proliferation as well as natural killer (NK) activity. Suppressive activity in media from cleaved and uncleaved ova did not differ significantly, and activity in media from transferred embryos was not correlated significantly with successful pregnancy. The implications of these data are discussed.

L18 ANSWER 4 OF 4 MEDLINE on STN
86320734. PubMed ID: 3752339. Production of immunosuppressor factor(s) by preimplantation human embryos. Daya S; Clark D A. American journal of reproductive immunology and microbiology : AJRIM, (1986 Jul) 11 (3) 98-101. Journal code: 8501543. ISSN: 8755-8920. Pub. country: United States. Language: English.
AB Embryonic loss prior to implantation appears to be a significantly frequent phenomenon and this is further reinforced by the very low pregnancy rates reported by in vitro fertilization and embryo transfer programs. **Implantation failure** may possibly be the result of rejection of the antigenic embryo by the hostile maternal immune system. The mechanism by which embryos in successful pregnancies escape these rejection responses may depend upon their ability to produce factor(s) that suppress in vitro mitogen-induced lymphocyte proliferation. Only 43% of cleaved embryos demonstrated this ability. We postulate that successful pregnancies are dependent upon the production by embryos of immunosuppressor factor(s) that has a direct suppressive effect on the maternal immune response.

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=> s l20 and infertility
L21 1 L20 AND INFERTILITY

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L21 ANSWER 1 OF 1 MEDLINE on STN
91059924. PubMed ID: 2245843. Analysis of immunosuppressive molecules associated with murine in vitro fertilized embryos. Porat O; **Clark D A**. (Department of Medicine, McMaster University, Hamilton, Ontario, Canada.) Fertility and sterility, (1990 Dec) 54 (6) 1154-61. Journal code: 0372772. ISSN: 0015-0282. Pub. country: United States. Language:

English.

AB Supernatants from mouse in vitro fertilized (IVF) oocyte cultures may suppress in vitro lymphocyte proliferation stimulated by concanavalin A (Sigma, St. Louis, MO). Supernatants conditioned by incubation with mouse epididymal sperm alone were even more inhibitory. Thin-layer chromatography suggested the polyamines spermine in sperm and spermine plus spermidine in IVF embryo supernatants were responsible. Putrescine was not suppressive. In vitro fertilized oocytes from old CBA/J-strain mice (greater than 20 weeks) that suffer age onset **infertility** lacked suppression and manifest cleavage arrest that could be partially reversed by adding spermine to the cultures. The failure of IVF oocytes to produce adequate quantities of polyamines could lead to failure of implantation due to division arrest. A possible in vivo role of polyamines as immunosuppressor factors is discussed.

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L22 30 DUP REMOVE L20 (1 DUPLICATE REMOVED)

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L22 ANSWER 1 OF 30 MEDLINE on STN
2003549563. PubMed ID: 14629022. Placental trophoblast from successful human pregnancies expresses the tolerance signaling molecule, CD200 (OX-2). **Clark David A**; Keil Anja; Chen Zhiqi; Markert Udo; Manuel Justin; Gorczynski Reginald M. (Department of Medicine, McMaster University, Hamilton, Ontario, Canada.. clarkd@mcmaster.ca) . American journal of reproductive immunology (New York, N.Y. : 1989), (2003 Sep) 50 (3) 187-95. Journal code: 8912860. ISSN: 1046-7408. Pub. country: Denmark. Language: English.

AB PROBLEM: Th1 cytokine-dependent abortions in the CBA x DBA/2 mouse model have been linked to down-regulation of expression of the CD200 (OX-2) 'tolerance' signal on trophoblast and in decidua prior to onset of the abortion process. Abortions could be prevented by administration of a soluble CD200. Is CD200 expressed on trophoblast in successful human pregnancy? METHOD OF STUDY: As one cannot easily obtain trophoblasts in large quantities from successful human pregnancies in the first trimester prior to the onset of the abortion process at 6 weeks gestation, we examined as a first step, trophoblast isolated from term placentae (i.e. successful pregnancies). CD9- trophoblasts were isolated by affinity column and stained for intracellular cytokeratin, and surface CD200 using PE-anti-human CD200 monoclonal antibody. mRNA was extracted from CD9+ and CD9- cells and tested by reverse transcription-polymerase chain reaction for CD200 mRNA. CD9- placental cells were separated by velocity sedimentation and test for CD200-dependent suppression of an allogeneic human mixed lymphocyte culture where cytotoxic T cell (CTL) generation, and Th1 --> Th2 cytokine production shift were measured. RESULTS: CD9- but not CD9+ placental cell populations contained cells with mRNA for CD200, both a normal length transcript and a truncated transcript. Flow cytometry showed a CD200+ cytokeratin+ moderate-to-large-sized cell population compatible with trophoblasts and a smaller subset of cytokeratin- cells that expressed CD200 at normal and at high levels. The moderate-sized population proved most potent at inhibiting CTL generation and caused a Th1 --> Th2 cytokine shift. These effects were blocked by monoclonal anti-CD200. CONCLUSIONS: A subpopulation of cytokeratin+ placental trophoblasts express bioactive CD200 able to alter maternal immune responses in a favorable (Th2 > Th1) direction. Two populations of CD200+ small- and medium-small-sized cytokeratin- placental cells remain to be identified. Studies of karyotyped first trimester elective termination and spontaneous miscarriage tissues are needed.

L22 ANSWER 2 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
2001:693368 Document No. 135:267229 Methods and compositions for

immunoregulation. Gorczynski, Reginald M.; **Clark, David A.** (Can.). PCT Int. Appl. WO 2001068697 A2 20010920, 83 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-CA346 20010316. PRIORITY: US 2000-PV189986 20000317.

AB Methods and compns. for inducing immune suppression are disclosed. The methods involve administering an effective amount of an agent that inhibits MD-1 with or without an OX-2 protein or a nucleic acid encoding an OX-2 protein. The methods are useful in preventing graft rejection, fetal loss, autoimmune disease, and allergies. Methods and compns. for preventing immune suppression are also disclosed. The methods involve administering an effective amount of MD-1 or an agent that activates or stimulates MD-1.

L22 ANSWER 3 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN

2001:687850 Document No. 136:245923 Does successful allopregnancy mimic transplantation tolerance?. Gorczynski, Reginald M.; Yu, Gary; **Clark, David A.** (RM CCRW-2-855, Toronto Hospital, Toronto, ON, M5G2C4, Can.). Graft (Thousand Oaks, CA, United States), 4(5), 338-345 (English) 2001. CODEN: GTOCA5. ISSN: 1522-1628. Publisher: Sage Science Press.

AB A review. The dendritic-cell associated mol. CD200 is up-regulated in rodent transplantation models where successful inhibition of rejection is accomplished. The mechanism by which CD200 achieves this effect involves signaling a receptor, CD200r, on macrophages and/or γδTCR+ cells, both of which have been implicated in adoptive transfer of tolerance. In addition to inhibition of rejection, increased expression of CD200 is associated with altered polarization in cytokine production, with increased expression of IL-4, IL-10 and TGFβ, and decreased IL-2, IFNγ and TNF-α. Inhibition of rejection can thus be adoptively transferred by IL-10/TGFβ and a CD200 immunoadhesin and in turn can be inhibited by neutralizing these cytokines or by functional blockade of CD200 expression. Successful pregnancy in allopregnant mice can also be viewed as dependent upon control of graft rejection. Proinflammatory Th1 cytokines (TNF-α + IFN-γ + IL-1) can cause spontaneous abortion in mice by a mechanism which involves a novel prothrombinase, fgl2, which promotes fibrin deposition. However, we found that spontaneous abortion rates in abortion-prone CBA + DBA/2 matings and in low abortion rate CBA + BALB/c matings were lower than the frequency of implantation sites showing fibrinhi + fgl2 mRNAhi. CD200 expression was present in the same sites as fgl2 mRNA, and neutralization of this CD200 expression by anti-CD200 antibody raised the abortion rate to predicted levels. Conversely, a CD200 immunoadhesin dramatically reduced the abortion rate. We hypothesize that in addition to its role in organ and tissue allograft rejection, CD200 expression is involved in the prevention of spontaneous abortion triggered by cytokine up-regulation of fgl2 at the feto-maternal interface.

L22 ANSWER 4 OF 30 MEDLINE on STN

2001385133. PubMed ID: 11437633. Procoagulants in fetus rejection: the role of the OX-2 (CD200) tolerance signal. **Clark D A**; Yu G; Levy G A; Gorczynski R M. (Departments of Medicine, Molecular Medicine & Pathology, Obstetrics & Gynecology, Mucosal Immunology Group, Immunology and Inflammation Program, McMaster University, Rm. 3V39, 1200 Main Street West, Hamilton, Ontario, L8N 3Z5, Canada.. clarkd@mcmaster.ca) . Seminars in immunology, (2001 Aug) 13 (4) 255-63. Ref: 45. Journal code: 9009458. ISSN: 1044-5323. Pub. country: United States. Language: English.

AB The spontaneous loss of normal karyotype embryos may be initiated or

prevented by the maternal immune system. In mice, loss between the time of implantation (day 4.5) and formation of a vascularized placenta (day 9.5) when the embryo is too large to survive by diffusion alone, is analogous to occult pregnancy failure in humans. They are called occult because usually the woman does not know she is pregnant. From studies in mice, these early losses have a different mechanism than abortion of a vascularized placenta (analogous to clinically evident human spontaneous miscarriage). The latter depend on the activation of the novel prothrombinase fgl2 on the fetal trophoblast and in maternal decidua by the T helper-1 (Th1) type cytokines TNF- alpha+gamma -interferon that arise from NK cells and NK gammadelta T cells; conversion of prothrombin to thrombin which in turn generates IL8 that activates polymorphonuclear leukocytes leads to embryonic death. These inflammatory processes are counteracted by Th2/3-type cytokines that arise in part from V gamma 1 delta 6 T cells reacting to, as yet, unidentified trophoblast antigens in the presence of the 'tolerance signaling molecule' OX-2. By contrast, peri-implantation losses (between implantation and formation of a vascularized placenta, analogous to occult losses in humans) appear to be dependent upon perforin(+)cells, complement activation, and products of alphabeta T and NK alphabeta T cells, but not on TNF- alpha or procoagulant activation. Similarities and differences between findings in the mouse and human, and the potential evolutionary significance of mechanisms affecting reproductive success are reviewed.

L22 ANSWER 5 OF 30 MEDLINE on STN DUPLICATE 1
2001033110. PubMed ID: 11046009. Receptor engagement on cells expressing a ligand for the tolerance-inducing molecule OX2 induces an immunoregulatory population that inhibits alloreactivity in vitro and in vivo. Gorczynski R M; Yu K; **Clark D**. (University Health Network, Toronto, Canada.) Journal of immunology (Baltimore, Md. : 1950), (2000 Nov 1) 165 (9) 4854-60. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Increased survival of C57BL/6 renal allografts following portal vein donor-specific pretransplant immunization of C3H mice is associated with increased expression of the molecule OX2 seen on host dendritic cells, along with a marked polarization in cytokine production from lymphocytes harvested from the transplanted animals, with preferential production of IL-4, IL-10, and TGF-beta on donor-specific restimulation in vitro, and decreased production of IL-2, IFN-gamma, and TNF-alpha compared with non-portal vein-immunized control transplanted mice. The increased renal allograft survival and the altered cytokine production are abolished by infusion of anti-mouse OX2 mAb (3B6). Infusion of a soluble OX2:Fc immunoadhesin can itself produce significant prolongation of xeno- and allografts in mice. We have used FITC-conjugated OX2:Fc to characterize cells expressing a ligand (OX2L) for OX2, and provide evidence that subpopulations of LPS-stimulated splenic macrophages, Con A-activated splenic T cells, and the majority (>80%) of gammadeltaTCR(+) T cells express this ligand. We show below that F4/80(+), OX2L(+) splenic macrophages, admixed with OX2:Fc, represent a potent immunosuppressive population capable of causing more profound inhibition of alloreactivity in vitro or in vivo than that seen using either OX2:Fc or OX2(+) (or OX2L(+)) cells alone. Immunoregulation by this OX2L(+) population occurs in an MHC-restricted fashion.

L22 ANSWER 6 OF 30 MEDLINE on STN
2000112274. PubMed ID: 10647748. Hard science versus phenomenology in reproductive immunology. **Clark D A**. (Department of Medicine, McMaster University, Hamilton, Ontario, Canada.) Critical reviews in immunology, (1999) 19 (5-6) 509-39. Ref: 253. Journal code: 8914819. ISSN: 1040-8401. Pub. country: United States. Language: English.

AB It has been suggested that studies of immunological aspects of reproduction have recently changed from the phenomenological (e.g., speculative/descriptive) to hard science (e.g., precise molecular

description/ explanation). The significance of this development is explored by analysis of the contribution made by hard science that has led to a number of assertions. Does HLA-G determine maternal tolerance of her semi-allogeneic fetus? Do differences in placentation between humans, rodents, and other species make direct comparisons largely meaningless? Does membrane cofactor protein (CD46) contribute to pregnancy success by protecting sperm and fetal trophoblast from complement-mediated lysis? Does a low frequency in mice of maternal T cells specific for paternal alloantigens occur, and if so, does phenomenon explain specific maternal tolerance in pregnancy? Do placental and decidual macrophage components provide an important immediate antigen-nonspecific host defense to infection? Does the mix of bioactive molecules make the uterus an immunologically privileged site, and does the molecular melange have a pivotal role in promoting growth and development of the placenta and embryo? Does prolactin acting on receptors on lymphocytes suppress function and thereby account for remission of autoimmune disease in pregnant women? Is the efficacy and safety of immunotherapy for recurrent spontaneous abortion a thorny issue that will be resolved by an ongoing funded national trial? What is a scientifically correct timeline of important discoveries and developments in reproductive immunology? It is argued that it is unprofitable to divorce phenomenology from hard science and that the timeline for developments in reproductive immunology begin with Darwin. Irrespective of whether one is dealing with phenomena or hard science data, Hippocrates was correct in his aphorism that "description is infinite and easy; explanation is limited and difficult".

L22 ANSWER 7 OF 30 MEDLINE on STN

95229873. PubMed ID: 7536211. CD56+ lymphoid cells in human first trimester pregnancy decidua as a source of novel transforming growth factor-beta 2-related immunosuppressive factors. **Clark D A**; Vince G; Flanders K C; Hirte H; Starkey P. (Department of Medicine, McMaster University, Hamilton, Ontario, Canada.) Human reproduction (Oxford, England), (1994 Dec) 9 (12) 2270-7. Journal code: 8701199. ISSN: 0268-1161. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The lymphomyeloid cells isolated from normal first trimester pregnancy decidua may be separated into a CD56+ population of natural killer (NK)-lineage cells with the morphology of granulated lymphocytes, and a CD56- population which includes other cell types. Unlike CD56+ NK cells in peripheral blood, decidual CD56+ cells lack type III Fc receptors (CD16) and did not express significant levels of either type I FcR (CD64) or type II FcR (CDw32). By contrast to the decidual CD56- cells, CD56+ cells could release biologically active transforming growth factor (TGF)-beta in vitro, detectable using an normal rat kidney fibroblast colony-forming assay. The CD56+ cells could be stained using an antibody specific for TGF-beta 2, and similarly staining cells could be detected in intact biopsies of normal pregnancy decidua. Bioactive TGF-beta is known to suppress the generation of cytotoxic cells in vitro, and high performance liquid chromatography fractionation of supernatants conditioned by CD56+ but not CD56- cells contained reproducible peaks of immunosuppressive activity at 40-45 and 15-20 kDa, similar to the TGF-beta 2 immunosuppressive activity in supernatants conditioned by unfractionated decidua.

L22 ANSWER 8 OF 30 MEDLINE on STN

94163705. PubMed ID: 8118884. Prevention of spontaneous abortion in DBA/2-mated CBA/J mice by GM-CSF involves CD8+ T cell-dependent suppression of natural effector cell cytotoxicity against trophoblast target cells. **Clark D A**; Chaouat G; Mogil R; Wegmann T G. (Department of Medicine, McMaster University, Hamilton, Ontario, Canada.) Cellular immunology, (1994 Mar) 154 (1) 143-52. Journal code: 1246405. ISSN: 0008-8749. Pub. country: United States. Language: English.

AB Spontaneous resorption (abortion) that occurs at a high rate in DBA/2-mated CBA/J female mice is dependent upon asialoGM1+ natural effector-type cells, can be ameliorated by alloimmunization or

administration of GM-CSF, and is augmented by in vivo injection of anti-CD8 antibody. The abortion rate was similarly augmented by administration of monoclonal anti-GM-CSF neutralizing antibody, but the GM-CSF physiologically active in preventing abortion during normal pregnancy did not appear to be derived from maternal CB8+ T cells putatively responding to antigens on the fetoplacental unit. Rather, depletion of CD8+ cells in vivo prevented GM-CSF from reducing the rate of resorptions. GM-CSF administration rapidly downregulates natural effector cells able to kill a trophoblast target cell line in vitro, and anti-CD8+ antibody boosts total splenic cytotoxic cell activity. Further, anti-CD8 completely abrogated the ability of GM-CSF to suppress anti-trophoblast killer cell activity. These cells are known to be asialoGM1+ and injection of anti-asialoGM1 reduced the abortion rate appropriately in mice that had received anti-CD8. These data suggest that GM-CSF acts indirectly to prevent abortion in DBA/2-mated CBA/J mice through a mechanism that requires CD8+ maternal T cells, and systemic regulation of the level of anti-trophoblast killer cell activity may determine the success or failure of pregnancy in this system.

L22 ANSWER 9 OF 30 MEDLINE on STN

91152748. PubMed ID: 1998971. Generation of lymphokine-activated killer cells in human ovarian carcinoma ascitic fluid: identification of transforming growth factor-beta as a suppressive factor. Hirte H; **Clark D A**. (Ontario Cancer Treatment and Research Foundation, Hamilton Regional Cancer Centre, Ontario, Canada.) Cancer immunology, immunotherapy : CII, (1991) 32 (5) 296-302. Journal code: 8605732. ISSN: 0340-7004. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB The effect of cell-free ascitic fluid from patients with epithelial ovarian carcinoma on the generation of lymphokine-activated killer cells (LAK) was compared to the activity generated in control medium containing 10% fetal bovine serum, using Daudi target cells. Samples of ascitic fluid from nine different patients tested inhibited LAK generation. Suppressive activity was evident as early as 24 h of incubation in the presence of ascitic fluid and increasing suppression developed with prolonged exposure. Suppression was concentration-dependent, present at 10%-20% and increasing with concentrations up to 80%. The suppressive effect of ascitic fluid was only partially reversed on increasing the concentration of interleukin-2 (IL-2) from 10 units to 1000 units/ml. Activated LAK appeared to maintain the majority of their activity on further culture in ascitic fluid in the presence of IL-2 but further enhancement of lytic activity was prevented. Fractionation of a suppressive sample by HPLC, using 0.1 M KCl/acetic acid buffer pH 2.6, revealed that the dominant peak of suppressive activity eluted at 25 kDa; with pH 7.0 TRIS-buffered saline, most of the activity was lost on the column. Antibody neutralization studies of the 25-kDa suppressive peak as well as on whole ascitic fluid have revealed that transforming growth factor beta (TGF beta) is the major suppressive factor present in ascitic fluid. Factors that suppress LAK generation in vitro were present in all samples tested. The effect on the lytic activity of activated LAK cells was minimal. This suggests that, in the clinical setting, the greatest impact would be achieved by activating LAK cells ex vivo and subsequently transferring them to the peritoneal cavity in the presence of IL-2 rather than by attempting to generate them in situ by injecting IL-2 into the peritoneal cavity. However, reversal of TGF beta-mediated suppression in situ may be necessary to allow local proliferation of LAK cells to achieve an effective killer-to-target ratio.

L22 ANSWER 10 OF 30 MEDLINE on STN

90217505. PubMed ID: 2182711. Murine pregnancy decidua produces a unique immunosuppressive molecule related to transforming growth factor beta-2. **Clark D A**; Flanders K C; Banwatt D; Millar-Book W; Manuel J; Stedronska-Clark J; Rowley B. (Molecular Virology and Immunology Program, McMaster University, Hamilton, Ontario, Canada.) Journal of immunology

(Baltimore, Md. : 1950), (1990 Apr 15) 144 (8) 3008-14. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Non-T small lymphocytic suppressor cells in murine allopregnancy release a potent immunosuppressive factor in vitro that is neutralized by rabbit anti-transforming growth factor (TGF)-beta. Previous studies have suggested that the decidual suppressor factor (DSF) is smaller than TGF-beta 1, and in this paper, we show that DSF on HPLC-sieving columns also elutes later than TGF-beta 2. Nevertheless, DSF has the ability to promote anchorage-independent growth of NRK fibroblasts similar to TGF-beta s. Using turkey antibodies specific for TGF-beta 1 or beta 2, we show that DSF is related to TGF-beta 2 rather than TGF-beta 1, and this relationship was confirmed by using a panel of murine mAb to TGF-subtypes. PAGE and Western blotting showed that the TGF-beta 2-reactive molecules in HPLC-purified DSF was slightly smaller than TGF-beta 2 and approximately 20 to 23 kDa. The DSF molecule is therefore closely related to TGF-beta 2 but as released from decidua, differs in size. The TGF-beta 2-related decidual suppressor factor was also obtained from the decidua of synpregnant C.B.-17 severe combined immune deficiency (SCID) and pregnant SCID-BG (C57BL/6 background) mice, confirming the lack of T or B cell dependence of DSF production and the generality of production of a TGF-beta-related suppressor factor by decidua associated with successful pregnancy in mice.

L22 ANSWER 11 OF 30 MEDLINE on STN

91059924. PubMed ID: 2245843. Analysis of immunosuppressive molecules associated with murine in vitro fertilized embryos. Porat O; **Clark D A**. (Department of Medicine, McMaster University, Hamilton, Ontario, Canada.) Fertility and sterility, (1990 Dec) 54 (6) 1154-61. Journal code: 0372772. ISSN: 0015-0282. Pub. country: United States. Language: English.

AB Supernatants from mouse in vitro fertilized (IVF) oocyte cultures may suppress in vitro lymphocyte proliferation stimulated by concanavalin A (Sigma, St. Louis, MO). Supernatants conditioned by incubation with mouse epididymal sperm alone were even more inhibitory. Thin-layer chromatography suggested the polyamines spermine in sperm and spermine plus spermidine in IVF embryo supernatants were responsible. Putrescine was not suppressive. In vitro fertilized oocytes from old CBA/J-strain mice (greater than 20 weeks) that suffer age onset infertility lacked suppression and manifest cleavage arrest that could be partially reversed by adding spermine to the cultures. The failure of IVF oocytes to produce adequate quantities of polyamines could lead to failure of implantation due to division arrest. A possible in vivo role of polyamines as immunosuppressor factors is discussed.

L22 ANSWER 12 OF 30 MEDLINE on STN

91012367. PubMed ID: 2213723. Decidua-associated suppressor activity and viability of individual implantation sites of allopregnant C3H mice. **Clark D A**; Drake B; Head J R; Stedronska-Clark J; Banwatt D. (Molecular Virology and Immunology Program, McMaster University, Hamilton, Ontario, Canada.) Journal of reproductive immunology, (1990 Jun) 17 (3) 253-64. Journal code: 8001906. ISSN: 0165-0378. Pub. country: Netherlands. Language: English.

AB Release of soluble suppressor activity from individual implant site decidua of DBA/2-mated C3H/HeJ mice was measured on days 12.5-13.5 of pregnancy. Suppressor activity varied among sites and followed a distribution curve that was displaced towards low suppression when resorption sites were compared to healthy embryonic implants. Pre-immunization against the DBA/2 strain paternal antigens failed to increase resorption (by loss of low suppression implants) but led instead to a reduced resorption rate. This was associated with an increase in soluble suppressor activity obtained from decidua. Some reduction in resorption occurred independent of an increase in the level of suppression suggesting additional contributing factors to the immunization effect.

L22 ANSWER 13 OF 30 MEDLINE on STN
90356898. PubMed ID: 2202033. Are there immune abortions?. **Clark D A**. (Department of Medicine Obstetrics and Gynecology, McMaster University, Hamilton, Ontario, Canada.) Research in immunology, (1990 Feb) 141 (2) 202-7. Ref: 43. Journal code: 8907467. ISSN: 0923-2494. Pub. country: France. Language: English.

L22 ANSWER 14 OF 30 MEDLINE on STN
90027293. PubMed ID: 2679751. Cytokines and pregnancy. **Clark D A**. (Molecular Virology and Immunology Program, McMaster University, Hamilton, Ontario, Canada.) Current opinion in immunology, (1989 Aug) 1 (6) 1148-52. Ref: 21. Journal code: 8900118. ISSN: 0952-7915. Pub. country: United States. Language: English.

L22 ANSWER 15 OF 30 MEDLINE on STN
89349273. PubMed ID: 2475019. Histologic and immunologic study of uterine biopsy tissue of women with incipient abortion. Michel M; Underwood J; **Clark D A**; Mowbray J F; Beard R W. (Department of Obstetrics and Gynaecology, St. Mary's Hospital Medical School, London, England.) American journal of obstetrics and gynecology, (1989 Aug) 161 (2) 409-14. Journal code: 0370476. ISSN: 0002-9378. Pub. country: United States. Language: English.

AB Biopsy specimens taken from the region of the placental bed were examined for the presence of phloxinophilic granulated mononuclear cells in women with a history of recurrent miscarriage and who would eventually miscarry a current pregnancy. They were compared with biopsy specimens from women with intact pregnancies presenting for elective termination of pregnancy and those with "missed abortion." Cells with large cytoplasmic granules (greater than or equal to 1 micron) were abundant in the group of ongoing pregnancies whereas cells with smaller granules (less than 1 micron) that were similar to large granular lymphocytes were more abundant relative to cells with large granules in the biopsy specimens from failing pregnancies. Immunosuppressive activity was tested in the supernatants of cultured biopsy samples of each group and found to be significantly lower in the incipient miscarriage group. These findings could represent alterations associated with the process of miscarriage, such as inflammation, or there may be deficient suppressor cell activity at the fetomaternal interface as the reason for "rejection" of the early embryo.

L22 ANSWER 16 OF 30 MEDLINE on STN
90003249. PubMed ID: 2529041. Hormone-induced preimplantation Lyt 2+ murine uterine suppressor cells persist after implantation and may reduce the spontaneous abortion rate in CBA/J mice. **Clark D A**; Brierley J; Banwatt D; Chaouat G. (Molecular Virology & Immunology Program, McMaster University, Hamilton, Ontario, Canada.) Cellular immunology, (1989 Oct 15) 123 (2) 334-43. Journal code: 1246405. ISSN: 0008-8749. Pub. country: United States. Language: English.

AB Immunoregulatory cells in the maternal uterine endometrium and decidua are thought to play an important role in ensuring the success of the semiallogeneic conceptus. Two phases of suppression have been described in pregnant mice. Prior to implantation, the hormonal changes triggered by mating activate or recruit a population of nonspecific Lyt 2+ suppressor cells that inhibit cytotoxic T lymphocyte generation: this suppression appears to wane at the time or implantation and 4-5 days after implantation, a non-T suppressor cell population activated or recruited by fetal trophoblast cells develops. In this paper we confirm the non-major histocompatibility complex specificity of the hormone-regulated preimplantation suppressor cell. We show that this activity persists in the uterus during the early postimplantation period where its suppressive activity is masked by an Fc-receptor-positive cell population recruited by the implanting embryo. The potential importance of the persisting suppressor cells is suggested by an increase in the rate of spontaneous abortion of DBA2-mated CBA/J mice following injection of monoclonal anti-Lyt 2+ antibody in the early postimplantation period.

L22 ANSWER 17 OF 30 MEDLINE on STN

89215515. PubMed ID: 2651541. Immunosuppressive activity in human in vitro fertilization (IVF) culture supernatants and prediction of the outcome of embryo transfer: a multicenter trial. **Clark D A**; Lee S; Fishell S; Mahadevan M; Goodall H; Ah Moye M; Schechter O; Stedronska-Clark J; Daya S; Underwood J; +. (McMaster University, Hamilton, Ontario, Canada.) Journal of in vitro fertilization and embryo transfer : IVF, (1989 Feb) 6 (1) 51-8. Journal code: 8412594. ISSN: 0740-7769. Pub. country: United States. Language: English.

AB The supernatants from cultured human oocytes fertilized in vitro contain low molecular weight factors that can suppress or stimulate the proliferative response of lymphocytes in vitro. The inhibitory and stimulatory effects are nonspecific and may be detected using cultured human or murine tumor cell lines. Using such a bioassay, we previously tested fetal cord serum-supplemented culture supernatant and found that an absence of suppression was correlated with an absence of subsequent pregnancy. To test this association further, additional samples were obtained from four different in vitro fertilization (IVF) units and studied blindly without knowledge of the pregnancy outcome. In this series, samples were obtained after the first 12-24 hr of sperm-oocyte incubation and all of the supernatants were from individual embryo cultures. The average number of preembryos transferred to those achieving pregnancy did not differ significantly from the number transferred to those not achieving pregnancy but the level of suppression was greater (8.7 +/- 1.9%) in those becoming pregnant compared to those not achieving pregnancy (0.8 +/- 1.5%). Twenty-two of 61 patients who received at least one embryo with a suppressive supernatant achieved pregnancy, whereas 0 of 19 patients received embryos lacking suppressive supernatants became pregnant. Two patients who received a single embryo from cultures with suppression became pregnant. Several problems with the bioassay method were defined. The culture medium in this series was always supplemented with adult serum, usually from the patient herself, and this serum could be suppressive.(ABSTRACT TRUNCATED AT 250 WORDS)

L22 ANSWER 18 OF 30 MEDLINE on STN

87225932. PubMed ID: 2953895. Characterization of hormone-dependent suppressor cells in the uterus of mated and pseudopregnant mice. Brierley J; **Clark D A**. Journal of reproductive immunology, (1987 Mar) 10 (3) 201-17. Journal code: 8001906. ISSN: 0165-0378. Pub. country: Netherlands. Language: English.

AB The survival of the implanted "fetal allograft" has been attributed to the action of local decidua-associated suppressor cells. These suppressor cells are Fc-receptor positive small lymphocytic cells lacking T-cell markers which arise following implantation, are localized at the implantation site, and block the action of IL-2 that stimulates NK and T effector cells. Kinetic studies have demonstrated the occurrence of an earlier peak of suppressive activity occurring 2-3 days after mating prior to implantation. The cells associated with pre-implantation suppression differs significantly from post-implantation suppressor cells. Velocity sedimentation studies show that early suppression is associated with large cells sedimenting at a modal velocity of 6-7 mm/hr. Suppressive activity from cells of similar size is also present in the uterine lining of hormonally-treated, pseudopregnant mice. In addition, suppressor cells can be demonstrated in the non-pregnant uterus at the time of estrus. These observations suggest suppressor cell activity may be hormonally regulated. The suppressor cell(s) in pseudopregnant mice bears Lyt 2.1 and Thy 1.2 surface antigens and suppressor(s) present in the pregnant animals bears Lyt 2.1 and Lyt 1.1. Although the suppressor cell was large, it did not appear to be a macrophage because it was resistant to antibodies to Mac-1 and FcR cell surface markers but susceptible to anti-T cell reagents. Furthermore, suppression was not mediated by a soluble factor that has been associated with the small lymphocytic suppressor. Thus, the suppressor activity present in the pre-implantation uterine

lining appears to differ significantly from the suppressor cell activity found after implantation. The possible role of a hormone-activated suppressor T cell in the success of the pregnancy is discussed.

L22 ANSWER 19 OF 30 MEDLINE on STN
87064919. PubMed ID: 3785315. Immunosuppressive factor (or factors) produced by human embryos in vitro. Daya S; **Clark D A**. New England journal of medicine, (1986 Dec 11) 315 (24) 1551-2. Journal code: 0255562. ISSN: 0028-4793. Pub. country: United States. Language: English.

L22 ANSWER 20 OF 30 MEDLINE on STN
87002605. PubMed ID: 2944622. Active suppression of host-versus-graft reaction in pregnant mice. VIII. The uterine decidua-associated suppressor cell is distinct from decidual NK cells. Slapsys R M; Richards C D; **Clark D A**. Cellular immunology, (1986 Apr 15) 99 (1) 140-9. Journal code: 1246405. ISSN: 0008-8749. Pub. country: United States. Language: English.
AB The fetus resulting from allogeneic mating expresses a variety of antigens that may serve as targets for rejection by the maternal immune system. Accumulation of non-T suppressor cells into the uterine decidua of allopregnant mice may serve to prevent such rejection. It has been previously shown that the suppressor activity in decidua during the second half of murine pregnancy is predominantly associated with a population of small lymphocytes with cytoplasmic granules that lack T-cell markers and inhibit the generation of cytotoxic lymphocytes (CTL) against paternal alloantigens both in vitro and in vivo. Since natural killer cells (NK) also possess cytoplasmic granules and may regulate the murine immune response, we examined the hypothesis that the decidua-associated non-T suppressor cell may represent a regulatory type of NK cell. Similar to NK cells, the decidua-associated suppressor cell expressed FcR for IgG. Unlike NK cells, the decidua-associated suppressor cell proved resistant to treatment with anti-asialo GM1 + C'. Sedimentation velocity examination demonstrated that decidua-associated NK activity was associated with cell population with a modal sedimentation of 4 mm/hr that was larger than the decidua-associated suppressor population. Potent suppressor cell activity was also recovered from the decidua of NK deficient allopregnant bg/bg mice. Therefore, decidua-associated NK cells and suppressor cells represent two distinct populations.

L22 ANSWER 21 OF 30 MEDLINE on STN
86320734. PubMed ID: 3752339. Production of immunosuppressor factor(s) by preimplantation human embryos. Daya S; **Clark D A**. American journal of reproductive immunology and microbiology : AJRIM, (1986 Jul) 11 (3) 98-101. Journal code: 8501543. ISSN: 8755-8920. Pub. country: United States. Language: English.
AB Embryonic loss prior to implantation appears to be a significantly frequent phenomenon and this is further reinforced by the very low pregnancy rates reported by in vitro fertilization and embryo transfer programs. Implantation failure may possibly be the result of rejection of the antigenic embryo by the hostile maternal immune system. The mechanism by which embryos in successful pregnancies escape these rejection responses may depend upon their ability to produce factor(s) that suppress in vitro mitogen-induced lymphocyte proliferation. Only 43% of cleaved embryos demonstrated this ability. We postulate that successful pregnancies are dependent upon the production by embryos of immunosuppressor factor(s) that has a direct suppressive effect on the maternal immune response.

L22 ANSWER 22 OF 30 MEDLINE on STN
87102923. PubMed ID: 3492277. Characterization of the cellular basis for the inhibition of cytolytic effector cells by murine placenta. **Clark D A**; Chaouat G. Cellular immunology, (1986 Oct 1) 102 (1) 43-51. Journal code: 1246405. ISSN: 0008-8749. Pub. country: United States. Language: English.

AB Direct suppression of cytolytic effector cell function by cells of the placenta may represent one mechanism that protects the "fetal allograft" from rejection by maternal transplantation immunity. Collagenase disaggregated murine placental cells block target cell lysis by natural killer, lymphokine-activated killer, and (CTL)-type killer cells. This inhibition is reversible and noncompetitive, similar to a previously described inhibitor of CTL found in spleens of mice undergoing an acute graft vs host (GVH) response. Velocity sedimentation separation of placental cells shows that the inhibitory activity is primarily associated with cells that cosediment with nucleated fetal erythrocytes. When these erythrocytes were lysed, an increased number of non-erythrocytic cells could be separated and under this circumstance, inhibitory activity was seen in association with either small white cells or fetal erythrocytes and with large white cells. There may be several cell populations in murine placenta that can inhibit cytolytic effector cells. The possible relevance of direct placental inhibition of cytolytic effectors to protection of the "fetal allograft" is discussed.

L22 ANSWER 23 OF 30 MEDLINE on STN

86011144. PubMed ID: 3876431. Effects of alterations in the immunocompetent status of Mus musculus females on the survival of transferred Mus caroli embryos. Croy B A; Rossant J; **Clark D A**. Journal of reproduction and fertility, (1985 Jul) 74 (2) 479-89. Journal code: 0376367. ISSN: 0022-4251. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The role of the immune system in promoting the midterm death of Mus caroli embryos transferred to the Mus musculus uterus was studied in vivo by transferring M. caroli blastocysts to recipients with altered immune status. Transfers of embryos to chimaeric mothers (Mus musculus in equilibrium Mus caroli), which were expected to be tolerant of species antigens, resulted in survival of M. musculus embryos but death of M. caroli embryos. The preferential survival of M. musculus embryos was explained by showing that M. musculus embryos can survive in the M. caroli uterus. Transfers to T cell-deficient mice of genotype nu/nu and to NK cell-deficient mice of genotype bg/bg as well as treatment of normal transfer recipients with Cyclosporin A or anti-Ia antiserum failed to prolong survival. However, immunization of recipients with M. caroli lymphocytes promoted more rapid and uniform failure of the interspecies pregnancy. Cytotoxic cells were detected in the resorbing embryos on Day 10.5 in immune pregnancies and on Day 12.5 in non-immune pregnancies and these cells were promiscuous in their pattern of lysis, showing equal reactivity against M. caroli, transfer recipient and 3rd party target cells. These experiments show that failure of M. caroli embryos in the M. musculus uterus is complex, but probably does not involve responses by classical cytotoxic T lymphocyte or natural killer cell pathways. Participation of the immune system in the resorption process, however, is confirmed and is associated with generation of promiscuous cytolytic cells.

L22 ANSWER 24 OF 30 MEDLINE on STN

84200763. PubMed ID: 6232864. Local active suppression by suppressor cells in the decidua: a review. **Clark D A**; Slapsys R; Croy B A; Krcek J; Rossant J. American journal of reproductive immunology : AJRI : official journal of the American Society for the Immunology of Reproduction and the International Coordination Committee for Immunology of Reproduction, (1984 Mar) 5 (2) 78-83. Ref: 74. Journal code: 8111069. ISSN: 0271-7352. Pub. country: United States. Language: English.

AB The immunological survival of the antigen-bearing mammalian feto-placental unit is determined by the functional properties of the tissues at the feto-maternal interface. Antigen-specific systemic suppressor mechanisms such as suppressor T cells and nonantigen-specific suppressive serum factors appear not to play a major role in protection of the fetus. A novel type of non-MHC specific suppressor cell accumulates locally in the decidua of successfully allopregnant mice. This decidua-associated

suppressor is a small lymphocytic cell possessing cytoplasmic granules, lacks T cell markers, and is deficient in number and activity at the implantation sites of viable xenogeneic Mus caroli embryos gestating in the uterus of Mus musculus animals at the time that maternal lymphoid cells begin to infiltrate the xenoembryos. These Mus caroli embryos subsequently resorb. Further experimental studies suggest that the trophoblast cells associated with successful pregnancy recruit bone-marrow derived maternal non-T suppressor cells to the decidua and thus, by an indirect mechanism, may act to protect the fetus from effector cells of the mother's immune system.

L22 ANSWER 25 OF 30 MEDLINE on STN
83084006. PubMed ID: 6184408. Pichinde virus-specific cell-associated suppression of primary footpad swelling in an inbred strain of Syrian hamsters. Chan M; **Clark D**; Rawls W E. Journal of immunology (Baltimore, Md. : 1950), (1983 Feb) 130 (2) 925-31. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.
AB Pichinde virus causes a lethal disease after i.p. inoculation of adult MHA hamsters; other strains of Syrian hamsters are resistant to this lethal infection. During studies of cell-mediated immune responses to Pichinde virus, it was noted that MHA hamsters survived infection when the virus was given in the footpad. However, unlike the resistant LSH and LVG strains of hamsters, the MHA hamsters did not manifest a footpad swelling response. Failure of the MHA hamster to respond to a footpad inoculation of Pichinde virus was shown to be virus-specific and appeared to be mediated by a cell-associated suppressor mechanism.

L22 ANSWER 26 OF 30 MEDLINE on STN
83250209. PubMed ID: 6603036. Nonspecific suppression of in vitro generation of cytotoxic lymphocytes by allogeneic and xenogeneic embryonic tissues. Croy B A; Rossant J; **Clark D A**; Wegmann T G. Transplantation, (1983 Jun) 35 (6) 627-9. Journal code: 0132144. ISSN: 0041-1337. Pub. country: United States. Language: English.

L22 ANSWER 27 OF 30 MEDLINE on STN
84113416. PubMed ID: 6663258. Interspecific hybrids and chimeras in mice. Rossant J; Croy B A; **Clark D A**; Chapman V M. Journal of experimental zoology, (1983 Nov) 228 (2) 223-33. Journal code: 0375365. ISSN: 0022-104X. Pub. country: United States. Language: English.
AB Interspecific hybrids and chimeras in mammals provide unique tools for investigating problems in genetics and embryology, because of the degree of disparity between the two component genotypes. We have attempted to produce hybrids and chimeras between Mus musculus, the laboratory mouse, and Mus caroli, a wild species of mouse from Southeast Asia. M. musculus and M. caroli do not normally interbreed, although sterile hybrids can be produced at a low rate by artificial insemination. Extrinsic problems of genotypic incompatibility between the fetus and the maternal environment seem to be involved in poor hybrid survival, since M. caroli blastocysts also die when transferred to the M. musculus uterus. Death is associated with the generation of maternal T-cells which are cytotoxic to M. caroli target cells in vitro. It is not yet clear whether this immune response is the primary cause of death or is secondary to breakdown of some other components of the fetal-maternal interaction. It is clear, however, that it is the trophoblast layer that mediates survival or death of the foreign embryonic cells in the M. musculus juterus, since M. caroli inner cell mass cells can survive to term after injection into M. musculus blastocysts: Viable interspecific chimeras result. Even more convincing evidence is provided by the production of viable M. caroli offspring by trophoblast vesicle reconstitution using trophoblast of M. musculus genotype and inner-cell mass of M. caroli type. Studies of properties of isolated trophoblast tissues have indicated that M. caroli trophoblast may differ from M. musculus in both its antigenic and immunosuppressive properties. Elucidation of trophoblast-uterine interactions in these various interspecific pregnancies is being aided by the development of an

in situ marker system, which can distinguish cells of the two species in sectioned material by in situ hybridization with a M. musculus satellite DNA probe. This same marker is also proving a very powerful tool for analyzing cell lineage development in chimeras.

L22 ANSWER 28 OF 30 MEDLINE on STN
83228655. PubMed ID: 6222661. Active suppression of host-versus-graft reaction in pregnant mice. V. Kinetics, specificity, and in vivo activity of non-T suppressor cells localized to the genital tract of mice during first pregnancy. Slapsys R; **Clark D A**. American journal of reproductive immunology : AJRI : official journal of the American Society for the Immunology of Reproduction and the International Coordination Committee for Immunology of Reproduction, (1983 Mar) 3 (2) 65-71. Journal code: 8111069. ISSN: 0271-7352. Pub. country: United States. Language: English.

L22 ANSWER 29 OF 30 MEDLINE on STN
83065279. PubMed ID: 6216485. Enhanced suppressor cell activity as a mechanism of immunosuppression by 2,3,7,8-tetrachlorodibenzo-p-dioxin. **Clark D A**; Gauldie J; Szewczuk M R; Sweeney G. Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N. Y.), (1981 Nov) 168 (2) 290-9. Journal code: 7505892. ISSN: 0037-9727. Pub. country: United States. Language: English.

L22 ANSWER 30 OF 30 MEDLINE on STN
80222908. PubMed ID: 6446406. Impairment of host-versus-graft reaction in pregnant mice. II. Selective suppression of cytotoxic T-cell generation correlates with soluble suppressor activity and with successful allogeneic pregnancy. **Clark D A**; McDermott M R; Szewczuk M R. Cellular immunology, (1980 Jun) 52 (1) 106-18. Journal code: 1246405. ISSN: 0008-8749. Pub. country: United States. Language: English.

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1: Prog Clin Biol Res. 1981;70:403-12.

Etiology of immune infertility.

Prakash C.

Semen of mammalian species contains a built-in system to prevent immunologic sensitization of females against antigens of sperm and seminal plasma in spite of repeated coitus. This prevention of sensitization is likely to be due to the presence of a potent immune response inhibitor originating from one of the sex accessory glands of the male. The inhibitor has been only biologically characterized so far. Failure of this built-in system in the male results in immune response to seminal antigens in the female. This seminal immunity, when of the right kind and magnitude, results in clinical immune-fertility.

Publication Types:
- Review

PMID: 7031700 [PubMed - indexed for MEDLINE]

Display Abstract Show: 20 Sort Send to Text

1: Arch Gynecol Obstet. 1990;248(2):67-74.

Cellular sensitization against spermatic and seminal plasma antigens in women after intrauterine insemination.

Schroder W, Mallmann P, van der Ven H, Diedrich K, Krebs D.

Department of Obstetrics and Gynecology, University of Bonn, FRG.

Using an indirect lymphokine-assay, the leucocyte-migration-inhibition-test (LMI-test), the cellular sensitization of fertile and infertile patients before and after homologous and heterologous intrauterine insemination (IUI) was investigated. In this assay several preparations of spermatozoa ("washed"-, "swim-up"- and "pellet"-spermatozoa) in different concentrations (1, 5 and 10 x 10(6) sperms/ml culture medium) and seminal plasma were tested as antigen. In all investigated groups a cellular immune response against spermatic antigen was demonstrable and seemed to be dose dependent. In contrast to fertile women who reacted with an enhancement of the macrophage migration for low concentrations the same concentration of antigen induced an inhibition of macrophage migration in fertile patients. For high concentrations of spermatic antigens there was a difference in the intensity of cell-mediated immune response between fertile and infertile women. Since infertile patients demonstrated an increased level of cell-mediated immune response it is possible that infertility may be caused by this altered immunological reaction. This response changes after multiple IUI-treatment and that change might be caused by the high concentration of spermatic antigens as there was a difference in the intensity of cell-mediated immune response between fertile and infertile women. Since infertile patients demonstrated an increased level of cell-mediated immune response it is possible that infertility may be caused by this altered immunological reaction. This response changes after multiple IUI-treatment and that change might be caused by the high concentration of spermatozoa. The immunological response of infertile patients seems to be similar in those receiving husband and donor IUI.

PMID: 2078059 [PubMed - indexed for MEDLINE]

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Erratum in:

- Am J Reprod Immunol 1994 Oct;32(3):255.

Comment in:

- Am J Reprod Immunol. 1994 Sep;32(2):53-4.

Worldwide collaborative observational study and meta-analysis on allogenic leukocyte immunotherapy for recurrent spontaneous abortion. Recurrent Miscarriage Immunotherapy Trialists Group.

[No authors listed]

PROBLEM: Recurrent spontaneous abortion (RSA) is a common complication of pregnancy for which there is no known cure. Therefore, effective treatment is needed. Published results from controlled clinical trials of allogeneic leukocyte immunization of women suffering from RSA have given conflicting results. To address this controversy, the international raw data of all patients who had been entered into clinical trials that included a control group were collected and analyzed. The primary question to be answered was whether alloimmune stimulation of the female partner improves the subsequent live birth rate. METHODS: Fifteen clinical centers were identified worldwide because they controlled appropriate raw data. Consequently, nine randomized trials (seven double-blinded) were evaluated independently by two separate data analysis teams to assure conclusions were robust. One team also compared randomized trials to the results of six nonrandomized cohort-controlled studies to test for bias in nonrandomized trials. Factors predicting successful live births among couples with RSA were evaluated by logistic regression. RESULTS: Although the two independent analyses made use of different definitions and utilized different statistical methods, the results of both were similar. The live births ratios (ratio of live births in treatment and control groups) with 95% confidence intervals (CI) were 1.16 (CI, 1.01-1.34, P = 0.031) and 1.21 (CI, 1.04-1.37, P = 0.024), respectively. The absolute differences in live birth rates between treatment and control groups were 8% and 10% in respective analyses. Results in randomized and nonrandomized trials were surprisingly similar despite significant differences in composition of control and treatment groups. Live birth rates were lower with older female partners, more than five abortions, with a positive ANA or with positive anticardiolipin

antibodies. Live birth rates were higher if the female partner had prior to treatment serum antibodies to paternal leukocytes or converted from negative to positive with immunization. Approximately 0.5% of controls and 2.1% of treated patients experience side effects for a 1.6% treatment related effect. There was no evidence of an increased risk of adverse effects on the fetus. CONCLUSIONS: Two independent analyses of worldwide data on allogeneic leukocyte immunization for treatment of RSA suggest that alloimmunization may be an effective treatment The treatment effect appears, however, to be small, and the data indicate that immunotherapy helps only 8% to 10% of affected couples. A current lack of diagnostic tests defining patients who most likely would benefit from immunotherapy, precludes the identification of a patient population that would benefit most from such treatment. The efficacy of treatment in such a subgroup could be expected to increase and could be of sufficient magnitude to allow the determination of more effective immunization protocols. This study does not exclude the possibility of a partial correction of a widely prevalent immunology defect by immunotherapy. The presence of such a defect would indicate a need for more effective therapy. The unexplained variation in pregnancy success rates of control groups among centers continues to present a statistical problem, limiting the statistical evaluation of retroactively obtained data.

Publication Types:

- Meta-Analysis
- Multicenter Study

PMID: 7826502 [PubMed - indexed for MEDLINE]

[Recurrent spontaneous abortion of alloimmunologic etiology--diagnosis and immunotherapy]

[Article in Polish]

Malinowski A.

Katedra Poloznictwa i Ginekologii Wojskowej Akademii Medycznej w Lodzi.

Alloimmunologic mechanisms have been implicated in a number of heretofore unexplained recurrent spontaneous abortions (RSA) and various forms of immunotherapy have been introduced to treat couples suffering from this condition. The treatment most widely used has been immunization using allogenic leukocytes from the partner. This immunotherapy is offered by many medical centers in the USA and elsewhere, although its efficacy remains controversial. Published trials and meta-analyses of published and unpublished studies have yielded conflicting results (success rate 57%-87%). The multicenter study performed under the auspices of the American Society of Reproductive Immunology concluded that contradictory results of investigations could be caused by the heterogeneity of study groups. Because of controversy about the efficacy of allogeneic leukocytes immunization for treatment of RSA, intravenous immunoglobulin as an alternative treatment have been sought. Small number of randomized, controlled trials of IVIG for treatment of RSA have been published. Although these results show that IVIG is effective in the treatment of RSA (live birth rate of 61-85%), it still is not clear what the ideal dosage is, and how frequently and how long IVIG therapy should be given.

Publication Types:
- Review
- Review, Tutorial

PMID: 11848031 [PubMed - indexed for MEDLINE]

1: Am J Reprod Immunol. 1992 Oct-Dec;28(3-4):281-4.

Immunotherapy of habitual abortion.

Carp HJ, Toder V, Mashiach S.

Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Israel.

Many cases of habitual abortion have been assumed to be due to hyporesponsiveness to the spouse's antigens encountered in pregnancy. Immunization by paternal leukocytes has been used to potentiate the immune response and prevent further miscarriages. This treatment has been highly controversial in terms of efficacy, mode of action, and side effects. More recently immunoglobulin has been used as passive immunization for similar indications. In our experience immunotherapy is effective; 80% of patients have subsequent live births. The most significant results are seen in patients with five or more abortions, in whom 66% of subsequent pregnancies develop normally compared to 20% in a control group. We have used antipaternal complement-dependent antibody (APCA) production after immunization as a marker of immune response. APCA correlates with beneficial outcome in the next pregnancy. APCA may also be associated with cytokines, which may enhance embryonic and trophoblast development. Immunoglobulin may similarly provide the relevant antibodies or cytokines. At present a large scale meta-analysis is being performed to confirm or refute the efficacy of this treatment. This meta-analysis may resolve the controversy.

Publication Types:

- Review
- Review, Tutorial

PMID: 1285902 [PubMed - indexed for MEDLINE]

Mechanisms of active suppression of the immune response to spermatozoa.

Witkin SS.

Dept. of Obstetrics and Gynecology, Cornell University Medical College, New York, NY 10021.

The production of autoantibodies to spermatozoa in males and isoantibodies in females is inhibited both by the physical isolation of spermatozoa from the systemic immune system and by active immunosuppression mechanisms. Lymphoid cells present in the epithelial lining of the rete testis, epididymis, and vas deferens, as well as the human ejaculate, are predominantly T suppressor/cytotoxic cells. Mononuclear cells derived from semen inhibit the in vitro activation of peripheral blood lymphocytes. Soluble specific T suppressor/cytotoxic cell activators in semen or on the sperm surface may be responsible for the predominance of this T cell subset in the male reproductive tract. The activation of T suppressor/cytotoxic cells following coitus may also limit the immune response to spermatozoa in females. Spermatozoa can also initiate immunosuppression, either by selectively inducing T suppressor cells or through the generation of activated complement components that block antibody production. Antisperm antibodies in sera from females may be associated with either a deficiency in the ability of their T suppressor/cytotoxic cells to be induced by factors in semen or by the occurrence in their husbands' ejaculates of microorganisms, antibodies, or other factors that induce T helper lymphocytes. Activated T cells produce interferon gamma, which induces Ia antigen expression on macrophages and allows the female's T helper cells to recognize processed sperm antigens. Recognition of the role of cell-mediated immune functions in the male and female genital tract identifies possible new target sites for the development of contraceptive agents.

Publication Types:
- Review
- Review, Tutorial

PMID: 2973252 [PubMed - indexed for MEDLINE]

1: Transplantation. 1978 Apr;25(4):216-20.

Maternal alloimmunisation in pregnancy. In vitro studies of T cell-dependent immunity to paternal alloantigens.

Smith JA, Burton RC, Barg M, Mitchell GF.

A secondary in vitro allograft reaction was used to demonstrate that spleen cells derived from allogeneically mated inbred mice were immunised against paternal alloantigens. In addition to the heightened alloantigen-specific in vitro response of these spleen cells, it was also found that spleen cells froma a wide variety of syngeneically and allogeneically mated mice were nonspecifically more reactive in the in vitro allograft reaction than spleen cells from virgin mice. However, when spleen cells freshly harvested from allogeneically mated mice were tested in a direct 51Cr release assay, lysis of target cells bearing the paternal alloantigens was demonstrable in only one-third of the experiments. It is proposed that T cell immunisation to paternal alloantigens occurs in pregnancy, but that cell-mediated cytotoxicity is inhibited.

PMID: 305673 [PubMed - indexed for MEDLINE]